L Number	Hits	Search Text	DB	Time stamp
-	596	serpin or granzyme ADJ inhibitor	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/18 09:03
-	328	granzyme	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/18 09:00
-	230092	inhibitor	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/18 09:00
-	11	granzyme NEAR inhibitor	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/18 09:04
-	593	serpin	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/18 09:03
-	4114	cytotoxic ADJ t ADJ cells	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/18 09:04
-	11602	(cytotoxic ADJ t ADJ cells) or ctl	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/18 09:04
-	5	(serpin or granzyme ADJ inhibitor) same ((cytotoxic ADJ t ADJ cells) or ctl)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/18 09:07
-	10	bleackley$.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/18 09:07

substituted polylysine were ineffective. Transfection with a plasmid encoding human factor IX produced expression in Hep G2 (high) and HuH7 cells that express SECR but not Hep G2 (low) cells that lack the receptor. Fluorescein-labeled C1315 peptide labeled 9-31% of Hep G2 (high), 10-14% of HuH7, and 0.6-3.4% of Hep G2 (low) cells, and when the lac Z gene was transfected, only these cells expressed beta-galactosidase. SECR-mediated gene transfer gives efficient, specific uptake and high-level expression of three reporter genes, and the system merits further study for **gene therapy**.

=> d his

(FILE 'HOME' ENTERED AT 09:29:48 ON 18 MAR 2003)

FILE 'MEDLINE, CAPLUS, EMBASE, BIOSIS' ENTERED AT 09:30:09 ON 18 MAR 2003

L1	88979	S	GENE THERAPY
L2	3193730	S	REVIEW
L3	54069	S	CTL OR CYTOTOXIC T CELLS
L4	61025	S	CTL OR CYTOTOXIC T CELL?
L5	22	S	L1 (S) L2 (S) L3 (S) L4
L6	13258	S	GRANZYME? INHIBITOR OR SERPIN OR P19 OR SP16
L7	0	S	L1 (S) L2 (S) L3 (S) L4 (S) L6
L8	0	S	L1 (L) L2 (L) L3 (L) L4 (L) L6
L9	0	S	L1 (S) L3 (S) L4 (S) L6
L10	0	S	L1 (S) L4 (S) L6
L11	0	S	L1 (L) L4 (L) L6
L12	62	S	L1 (L) L6
L13	0	S	L12 AND L3
L14	49	S	L1 (S) L6
L15	0	S	L1 (S) L6 (S) L2
L16	2	S	L1 (L) L6 (L) L2

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=> d his

     (FILE 'HOME' ENTERED AT 09:29:48 ON 18 MAR 2003)

     FILE 'MEDLINE, CAPLUS, EMBASE, BIOSIS' ENTERED AT 09:30:09 ON 18 MAR 2003
L1         88979 S GENE THERAPY
L2       3193730 S REVIEW
L3         54069 S CTL OR CYTOTOXIC T CELLS
L4         61025 S CTL OR CYTOTOXIC T CELL?
L5            22 S L1 (S) L2 (S) L3 (S) L4
L6         13258 S GRANZYME? INHIBITOR OR SERPIN OR P19 OR SP16
L7             0 S L1 (S) L2 (S) L3 (S) L4 (S) L6
L8             0 S L1 (L) L2 (L) L3 (L) L4 (L) L6
L9             0 S L1 (S) L3 (S) L4 (S) L6
L10            0 S L1 (S) L4 (S) L6
L11            0 S L1 (L) L4 (L) L6
L12           62 S L1 (L) L6
L13            0 S L12 AND L3
L14           49 S L1 (S) L6
L15            0 S L1 (S) L6 (S) L2
L16            2 S L1 (L) L6 (L) L2
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AE25CrmA and 293CrmA.

L14 ANSWER 48 OF 49 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:154174 BIOSIS
DOCUMENT NUMBER: PREV199900154174
TITLE: Development of animal models for adeno-associated virus site-specific integration.
AUTHOR(S): Rizzuto, Gabriella; Gorgoni, Barbara; Cappelletti, Manuela; Lazzaro, Domenico; Gloaguen, Isabelle; Poli, Valeria; Sgura, Antonella; Cimini, Daniela; Ciliberto, Gennaro; Cortese, Riccardo; Fattori, Elena; La Monica, Nicola (1)
CORPORATE SOURCE: (1) IRBM, P. Angeletti, 00040 Pomezia Italy
SOURCE: Journal of Virology, (March, 1999) Vol. 73, No. 3, pp. 2517-2526.
ISSN: 0022-538X.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The adeno-associated virus (AAV) is unique in its ability to target viral DNA integration to a defined region of human chromosome 19 (AAVS1). Since AAVS1 sequences are not conserved in a rodent's genome, no animal model is currently available to study AAV-mediated site-specific integration. We describe here the generation of transgenic rats and mice that carry the AAVS1 3.5-kb DNA fragment. To test the response of the transgenic animals to Rep-mediated targeting, primary cultures of mouse fibroblasts, rat hepatocytes, and fibroblasts were infected with wild-type wt AAV. PCR amplification of the inverted terminal repeat (ITR)-AAVS1 junction revealed that the AAV genome integrated into the AAVS1 site in fibroblasts and hepatocytes. Integration in rat fibroblasts was also observed upon transfection of a plasmid containing the rep gene under the control of the p5 and **p19** promoters and a dicistronic cassette carrying the green fluorescent protein (GFP) and neomycin (neo) resistance gene between the ITRs of AAV. The localization of the GFP-Neo sequence in the AAVS1 region was determined by Southern blot and FISH analysis. Lastly, AAV genomic DNA integration into the AAVS1 site in vivo was assessed by virus injection into the quadriceps muscle of transgenic rats and mice. Rep-mediated targeting to the AAVS1 site was detected in several injected animals. These results indicate that the transgenic lines are proficient for Rep-mediated targeting. These animals should allow further characterization of the molecular aspects of site-specific integration and testing of the efficacy of targeted integration of AAV recombinant vectors designed for human **gene therapy**.

L14 ANSWER 49 OF 49 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:438840 BIOSIS
DOCUMENT NUMBER: PREV199799738043
TITLE: Gene transfer into hepatoma cell lines via the serpin enzyme complex receptor.
AUTHOR(S): Ziady, Assem-Galal; Perales, Jose C.; Ferkol, Thomas; Gerken, Thomas; Beegen, Helga; Perlmutter, David H.; Davis, Pamela B. (1)
CORPORATE SOURCE: (1) Dep. Pediatrics, Case Western Reserve Univ., 11100 Euclid Ave., Cleveland, OH 44106 USA
SOURCE: American Journal of Physiology, (1997) Vol. 273, No. 2 PART 1, pp. G545-G552.
ISSN: 0002-9513.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The **serpin** enzyme complex receptor (SECR) expressed on hepatocytes binds to a conserved sequence in alpha-1-antitrypsin (alpha-1-AT) and other **serpins**. A molecular conjugate consisting of a synthetic peptide (C1315) based on the SECR binding motif of human (alpha-1-AT covalently coupled to poly-L-lysine was used to introduce reporter genes into hepatoma cell lines in culture. This conjugate condensed DNA into spheroidal particles 18-25 nm in diameter. When transfected with the SECR-directed complex containing pGL3, Hep G2 cells that express the receptor, but not Hep G2 cells that do not, expressed a peak luciferase activity of 538,731 +- 144,346 integrated light units/mg protein 4 days after transfection. Free peptide inhibited uptake and expression in a dose-dependent manner. Complexes of DNA condensed with polylysine or LC-sulfo-N-succinimidyl-3-(2-pyridyldithio)propionate-

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 NEWS  3  Apr 09  BEILSTEIN: Reload and Implementation of a New Subject Area
 NEWS  4  Apr 09  ZDB will be removed from STN
 NEWS  5  Apr 19  US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
 NEWS  6  Apr 22  Records from IP.com available in CAPLUS, MCAPLUS, and ZCAPLUS
 NEWS  7  Apr 22  BIOSIS Gene Names now available in TOXCENTER
 NEWS  8  Apr 22  Federal Research in Progress (FEDRIP) now available
 NEWS  9  Jun 03  New e-mail delivery for search results now available
 NEWS 10  Jun 10  MEDLINE Reload
 NEWS 11  Jun 10  PCTFULL has been reloaded
 NEWS 12  Jul 02  FOREGE no longer contains STANDARDS file segment
 NEWS 13  Jul 22  USAN to be reloaded July 28, 2002;
                  saved answer sets no longer valid
 NEWS 14  Jul 29  Enhanced polymer searching in REGISTRY
 NEWS 15  Jul 30  NETFIRST to be removed from STN
 NEWS 16  Aug 08  CANCERLIT reload
 NEWS 17  Aug 08  PHARMAMarketLetter(PHARMAML) - new on STN
 NEWS 18  Aug 08  NTIS has been reloaded and enhanced
 NEWS 19  Aug 19  Aquatic Toxicity Information Retrieval (AQUIRE)
                  now available on STN
 NEWS 20  Aug 19  IFIPAT, IFICDB, and IFIUDB have been reloaded
 NEWS 21  Aug 19  The MEDLINE file segment of TOXCENTER has been reloaded
 NEWS 22  Aug 26  Sequence searching in REGISTRY enhanced
 NEWS 23  Sep 03  JAPIO has been reloaded and enhanced
 NEWS 24  Sep 16  Experimental properties added to the REGISTRY file
 NEWS 25  Sep 16  CA Section Thesaurus available in CAPLUS and CA
 NEWS 26  Oct 01  CASREACT Enriched with Reactions from 1907 to 1985
 NEWS 27  Oct 21  EVENTLINE has been reloaded
 NEWS 28  Oct 24  BEILSTEIN adds new search fields
 NEWS 29  Oct 24  Nutraceuticals International (NUTRACEUT) now available on STN
 NEWS 30  Oct 25  MEDLINE SDI run of October 8, 2002
 NEWS 31  Nov 18  DKILIT has been renamed APOLLIT
 NEWS 32  Nov 25  More calculated properties added to REGISTRY
 NEWS 33  Dec 02  TIBKAT will be removed from STN
 NEWS 34  Dec 04  CSA files on STN
 NEWS 35  Dec 17  PCTFULL now covers WP/PCT Applications from 1978 to date
 NEWS 36  Dec 17  TOXCENTER enhanced with additional content
 NEWS 37  Dec 17  Adis Clinical Trials Insight now available on STN
 NEWS 38  Dec 30  ISMEC no longer available
 NEWS 39  Jan 13  Indexing added to some pre-1967 records in CA/CAPLUS
 NEWS 40  Jan 21  NUTRACEUT offering one free connect hour in February 2003
 NEWS 41  Jan 21  PHARMAML offering one free connect hour in February 2003
 NEWS 42  Jan 29  Simultaneous left and right truncation added to COMPENDEX,
                  ENERGY, INSPEC
 NEWS 43  Feb 13  CANCERLIT is no longer being updated
 NEWS 44  Feb 24  METADEX enhancements
 NEWS 45  Feb 24  PCTGEN now available on STN
 NEWS 46  Feb 24  TEMA now available on STN
 NEWS 47  Feb 26  NTIS now allows simultaneous left and right truncation
 NEWS 48  Feb 26  PCTFULL now contains images
 NEWS 49  Mar 04  SDI PACKAGE for monthly delivery of multifile SDI results

 NEWS EXPRESS  January 6 CURRENT WINDOWS VERSION IS V6.01a,
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                CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
                AND CURRENT DISCOVER FILE IS DATED 01 OCTOBER 2002
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=> s gene therapy
L1       88979 GENE THERAPY

=> s review
L2     3193730 REVIEW

=> s ctl or cytotoxic t cells
L3       54069 CTL OR CYTOTOXIC T CELLS

=> s ctl or cytotoxic t cell?
L4       61025 CTL OR CYTOTOXIC T CELL?

=> s l1 (S) l2 (S) l3 (S) l4
L5          22 L1 (S) L2 (S) L3 (S) L4

=> d 1-22 ibib abs

L5   ANSWER 1 OF 22     MEDLINE
ACCESSION NUMBER:   2003015583     IN-PROCESS
DOCUMENT NUMBER:    22409734   PubMed ID: 12522443
TITLE:              Principles of tumor immunosurveillance and implications for
                    immunotherapy.
AUTHOR:             Ochsenbein Adrian F
CORPORATE SOURCE:   [1] Department of Clinical Research, University of Berne,
                    Berne, Switzerland [2] Institute of Medical Oncology,
                    Inselspital, Berne, Switzerland.
SOURCE:             CANCER GENE THERAPY, (2002 Dec) 9 (12) 1043-55.
                    Journal code: 9432230. ISSN: 0929-1903.
```

PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20030111
Last Updated on STN: 20030111

AB Although antigen loss variants, major histocompatibility (MHC) class I down-regulation, or the expression of inhibitory molecules may explain the failure of immunosurveillance against some tumors, this seems not to apply for many other solid peripheral or lymphohematopoietic tumors. Why then is immunosurveillance so ineffective and can it be improved? This **review** focuses on one important aspect of tumor immunity, namely the relevance of antigen dose and localization. Immune responses in vivo are induced in organized lymphoid tissues, i.e., in lymph nodes and spleen. The antigen dose that reaches secondary lymphoid organs over time is a crucial parameter that drives antiviral and antitumoral immune responses. Tumors use various strategies to prevent efficient presentation of their antigens in lymphoid organs. A major obstacle to the induction of an endogenous tumor-specific cytotoxic T lymphocyte (**CTL**) response is the inefficient presentation of tumor antigen on MHC class I molecules of professional antigen-presenting cells. Peripheral solid tumors that develop outside lymphoid organs are, therefore, often ignored by the immune system. In other situations, tumors - especially of lymphohematopoietic origin - may tolerize specific **CTLs**. Understanding tumor immunosurveillance is key to the design of efficient antitumor vaccines. Attempts to improve immunity to tumors include vaccination strategies to (a) provide the tumor antigen to secondary lymphoid organs using recombinant viruses or dendritic cells as carriers, (b) express costimulatory signals on tumor cells, or (c) improve the efficiency of cross-priming. Cancer **Gene Therapy** (2002) 9, 1043-1055 doi:10.1038/sj.cgt.7700540

L5 ANSWER 2 OF 22 MEDLINE
ACCESSION NUMBER: 2002725601 IN-PROCESS
DOCUMENT NUMBER: 22376025 PubMed ID: 12489023
TITLE: Prospects for CD40-directed experimental therapy of human cancer.
AUTHOR: Tong Alex W; Stone Marvin J
CORPORATE SOURCE: Cancer Immunology Research Laboratory, Baylor Sammons Cancer Center, Baylor University Medical Center, Dallas, Texas 75246, USA.
SOURCE: CANCER GENE THERAPY, (2003 Jan) 10 (1) 1-13. Journal code: 9432230. ISSN: 0929-1903.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20021219
Last Updated on STN: 20021219

AB CD40, a member of the tumor necrosis factor receptor (TNF-R) family, is a surface receptor best known for its capacity to initiate multifaceted activation signals in normal B cells and dendritic cells (DCs). CD40-related treatment approaches have been considered for the experimental therapy of human leukemias, lymphomas, and multiple myeloma, based on findings that CD40 binding by its natural ligand (CD40L), CD154, led to growth modulation of malignant B cells. Recent studies also exploited the selective expression of the CD40 receptor on human epithelial and mesenchymal tumors but not on most normal, nonproliferating epithelial tissues. Ligation of CD40 on human breast, ovarian, cervical, bladder, non small cell lung, and squamous epithelial carcinoma cells was found to produce a direct growth-inhibitory effect through cell cycle blockage and/or apoptotic induction with no overt side effects on their normal counterparts. CD154 treatment also heightened tumor rejection immune responses through DC activation, and by increasing tumor immunogenicity through up-regulation of costimulatory molecule expression and cytokine production of epithelial cancer cells. These immunopotentiating features can produce a "bystander effect" through which the CD40-negative tumor subset is eliminated by activated tumor-reactive **cytotoxic T cells**. However, the potential risk of systemic inflammation and autoimmune consequences remains a concern for

systemic CD154-based experimental therapy. The promise of CD154 as a tumor therapeutic agent to directly modulate tumor cell growth, and indirectly activate antitumor immune response, may depend on selective and/or restricted CD154 expression within the tumor microenvironment. This may be achieved by inoculating cancer vaccines of autologous cancer cells that have been transduced ex vivo with CD154, as documented by recently clinical trials. This **review** summarizes recent findings on CD154 recombinant protein- and **gene therapy**-based tumor treatment approaches, and examines our understanding of the multifaceted molecular mechanisms of CD154-CD40 interactions.
doi:10.1038/sj.cgt.7700527

L5 ANSWER 3 OF 22 MEDLINE
ACCESSION NUMBER: 2002433493 IN-PROCESS
DOCUMENT NUMBER: 22177701 PubMed ID: 12189722
TITLE: Improvement of nonviral gene therapy by Epstein-Barr virus (EBV)-based plasmid vectors.
AUTHOR: Mazda O
CORPORATE SOURCE: Department of Microbiology, Kyoto Prefectural University of Medicine, Kamikyo, Kyoto 602-8566, Japan..
mazda@basic.kpu-m.ac.jp
SOURCE: Curr Gene Ther, (2002 Sep) 2 (3) 379-92.
Journal code: 101125446. ISSN: 1566-5232.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20020823
Last Updated on STN: 20021212
AB The nonviral gene transfer technologies include naked DNA administration, electrical or particle-mediated transfer of naked DNA, and administration of DNA-synthetic macromolecule complex vectors. Each method has its advantage, such as low immunogenicity, inexpensiveness, ease in handling, etc., but the common disadvantage is that the transfection efficiency has been relatively poor as far as conventional plasmid vectors are involved. To improve the nonviral gene transfer systems, Epstein-Barr virus (EBV)-based plasmid vectors (also referred to EBV-based episomal vectors) have been employed. These vectors contain the EBNA1 gene and oriP element that enable high transfer efficiency, strong transgene expression and long term maintenance of the expression. In the current article, I **review** recent preclinical **gene therapy** studies with the EBV plasmid vectors conducted against various diseases. For **gene therapy** against malignancies, drastic tumor suppression was achieved by gancyclovir administrations following an intratumoral injection with an EBV plasmid vector encoding the HSV1-TK suicide gene. Equiping the plasmid with carcinoembryonic antigen (CEA) promoter sequences enabled targeted killing of CEA-positive tumor cells, which was not accomplished by conventional plasmid vectors without the EBV genetic elements. Transfection with an apoptosis-inducing gene was also effective in inhibiting tumors. Interleukin (IL)-12 and IL-18 gene transfer, either local or systemic, induced therapeutic antitumoral immune responses including augmentation of the cytotoxic T lymphocyte (**CTL**) and natural killer (NK) activities, while an autologous tumor vaccine engineered to secrete Th1 cytokines via the EBV system also induced growth retardation of tumors. Non-EBV conventional plasmids were much less effective in eliciting these therapeutic outcomes. Intracardiomuscular transfer of the beta-adrenergic receptor gene induced a significant elevation in cardiac output in cardiomyopathic animals, suggesting the usefulness of the EBV system in treating heart failure. The EBV-based nonviral delivery also worked as genetic vaccine that triggered prophylactic cellular and humoral immunity against acute lethal viral infection. All the nonviral delivery vehicles so far tested showed an improved transfection rate when combined with the EBV-plasmids. Collectively, the EBV-based plasmid vectors may greatly contribute to nonviral **gene therapy** against a variety of disorders, including malignant, congenital, chronic and infectious diseases.

L5 ANSWER 4 OF 22 MEDLINE
ACCESSION NUMBER: 2002363265 MEDLINE
DOCUMENT NUMBER: 22104490 PubMed ID: 12109140

TITLE: Life or death of T cells with antigen-specific receptors--using T cells for cancer adoptive immunotherapy/gene therapy.
AUTHOR: Ren-Heidenreich L; Lum L G
CORPORATE SOURCE: Immunotherapy Program, Roger Williams Cancer Center, Providence, RI, USA.. lifenren@cs.com
SOURCE: Curr Gene Ther, (2001 Sep) 1 (3) 253-5. Ref: 29
Journal code: 101125446. ISSN: 1566-5232.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 20020712
Last Updated on STN: 20020801
Entered Medline: 20020731

AB A promising strategy for cancer treatment is adoptive **gene therapy**/immunotherapy by genetically modifying T lymphocytes with a chimeric receptor (ch-TCR) so that cytotoxic T lymphocytes (**CTL**) can target and lyse tumors in a MHC-non-restricted manner. It is, however, not clear whether non-MHC-restricted tumor cell recognition by T cells will result in activation-induced apoptosis (AICD). This **review** discusses the factors that affect the development of AICD or **CTL** proliferation, and how such factors should be considered in the design of clinical trials using ch-TCR.

L5 ANSWER 5 OF 22 MEDLINE
ACCESSION NUMBER: 2001672912 MEDLINE
DOCUMENT NUMBER: 21575473 PubMed ID: 11718942
TITLE: Pharmacotherapy by intracellular delivery of drugs using fusogenic liposomes: application to vaccine development.
AUTHOR: Kunisawa J; Nakagawa S; Mayumi T
CORPORATE SOURCE: Department of Biopharmaceutics, Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamadaoka, Suita, Osaka 565-0871, Japan.
SOURCE: Adv Drug Deliv Rev, (2001 Nov 19) 52 (3) 177-86. Ref: 53
Journal code: 8710523. ISSN: 0169-409X.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20011126
Last Updated on STN: 20020125
Entered Medline: 20020122

AB We prepared fusogenic liposomes by fusing conventional liposomes with an ultra-violet inactivated Sendai virus. Fusogenic liposomes can deliver encapsulated contents into the cytoplasm directly in a Sendai virus fusion-dependent manner. Based on the high delivery rates into the cytoplasm, we originally planned to apply the fusogenic liposomes to cancer chemotherapy and **gene therapy**. We have recently also examined the use of fusogenic liposomes as an antigen delivery vehicle. In terms of vaccine development, cytoplasmic delivery is crucial for the induction of the cytotoxic T lymphocyte (**CTL**) responses that play a pivotal role against infectious diseases and cancer. In this context, our recent studies suggested that fusogenic liposomes could deliver encapsulated antigens into the cytoplasm and induce MHC class I-restricted, antigen-specific **CTL** responses. In addition, fusogenic liposomes are also effective as a mucosal vaccine carrier. In this **review**, we present the feasibility of fusogenic liposomes as a versatile and effective antigen delivery system.

L5 ANSWER 6 OF 22 MEDLINE
ACCESSION NUMBER: 2001270314 MEDLINE
DOCUMENT NUMBER: 21260652 PubMed ID: 11368356
TITLE: Gene-based cancer vaccines: an ex vivo approach.

AUTHOR: Van Tendeloo V F; Van Broeckhoven C; Berneman Z N
CORPORATE SOURCE: Laboratory of Experimental Hematology, University Hospital, University of Antwerp, Belgium.
SOURCE: LEUKEMIA, (2001 Apr) 15 (4) 545-58. Ref: 196
Journal code: 8704895. ISSN: 0887-6924.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010604
Last Updated on STN: 20010604
Entered Medline: 20010531

AB The application of gene transfer techniques to immunotherapy has animated the field of gene-based cancer vaccine research. Gene transfer strategies were developed to bring about active immunization against tumor-associated antigens (TAA) through gene transfer technology. A wide variety of viral and nonviral gene transfer methods have been investigated for immunotherapeutic purposes. Ex vivo strategies include gene delivery into tumor cells and into cellular components of the immune system, including **cytotoxic T cells** and dendritic cells (DC).
The nature of the transferred genetic material as well as the gene transfer method has varied widely depending on the application. Several of these approaches have already been translated into clinical **gene therapy** trials. In this **review**, we will focus on the rationale and types of ex vivo gene-based immunotherapy of cancer. Critical areas for future development of gene-based cancer vaccines are addressed, with particular emphasis on use of DC and on the danger-tolerance hypothesis. Finally, the use of gene-modified DC for tumor vaccination and its prospects are discussed.

L5 ANSWER 7 OF 22 MEDLINE
ACCESSION NUMBER: 94102560 MEDLINE
DOCUMENT NUMBER: 94102560 PubMed ID: 8276260
TITLE: Somatic gene therapy for cancer: the utility of transferrinfection in generating 'tumor vaccines'.
AUTHOR: Zatloukal K; Schmidt W; Cotten M; Wagner E; Stingl G; Birnstiel M L
CORPORATE SOURCE: Research Institute of Molecular Pathology, I.M.P., Vienna, Austria.
SOURCE: GENE, (1993 Dec 15) 135 (1-2) 199-207. Ref: 65
Journal code: 7706761. ISSN: 0378-1119.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199402
ENTRY DATE: Entered STN: 19940218
Last Updated on STN: 19970203
Entered Medline: 19940210

AB The last few years have seen the development of a branch of somatic **gene therapy** which aims at strengthening the immune surveillance of the body, leading to eradication of disseminated cancer tumor cells and occult micrometastases after surgical removal of the primary tumor. Such a tumor vaccination protocol calls for cultivation of the primary tumor tissue and the insertion of one of three types of genes into the isolated cultured tumor cells followed by irradiation of the transfected or transduced cells to render them incapable of further proliferation. The cells so treated constitute the 'tumor vaccine'. A **review** of the literature suggests that for mouse models, in the initial period after inoculation, rejection of the tumor cells is usually effected by non-T-cell immunity, whereas the long-term systemic immune response is based on **cytotoxic T-cells**. High expression of the gene inserted into the tumor cells may be critical for the success of the vaccination procedure. Examples are given which indicate that transferrinfection, a procedure to introduce genes by

adenovirus-augmented receptor-mediated endocytosis, meets some important prerequisites for successful application of this type of **gene therapy**.

L5 ANSWER 8 OF 22 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:290147 CAPLUS
DOCUMENT NUMBER: 134:264742
TITLE: Possibility of immunotherapy against HIV infection
AUTHOR(S): Matsushita, Shuzo
CORPORATE SOURCE: AIDS Res. Cent., Kumamoto Univ., Japan
SOURCE: Tanpakushitsu Kakusan Koso (2001), 46(5), 638-643
CODEN: TAKKAJ; ISSN: 0039-9450
PUBLISHER: Kyoritsu Shuppan
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A **review** with 11 refs., on current status and future prospects in the treatment of HIV infection, discussing therapeutic strategies aiming at activation of cellular immunity against HIV, including **gene therapy** inducing **cytotoxic T cells**.

L5 ANSWER 9 OF 22 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:351290 CAPLUS
DOCUMENT NUMBER: 125:48019
TITLE: Gene therapy for HIV infection
AUTHOR(S): Bunnell, Bruce A.; Morgan, Richard A.
CORPORATE SOURCE: National Center Human Genome Research, National Institutes Health, Bethesda, MD, 20892, USA
SOURCE: Drugs of Today (1996), 32(3), 209-224
CODEN: MDACAP; ISSN: 0025-7656
PUBLISHER: Prous
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 112 refs. The ultimate goal of gene therapy for HIV-1 is to inhibit viral replication and the resultant AIDS pathogenesis. Gene therapy for HIV-1 requires the introduction of genes that effectively inhibit viral replication by blocking expression of viral genes or altering the normal function of HIV-1 assocd. proteins. This review details the various anti-HIV-1 gene therapy strategies that have been developed to effectively inhibit HIV-1 replication. The **review** covers three broad categories: (i) **gene therapy** using nucleic acid moieties such as gene vaccines, antisense DNA/RNA, RNA decoys, and ribosomes;(ii) protein approaches such as trans-dominant neg. proteins and single chain antibodies; and (iii) immunotherapy using HIV-1 specific **cytotoxic T cells**. The discussion focuses on the effectiveness of the various techniques in preclin. expts. and in animal models. Also, the status of all of the current RAC/FDA approved clin. protocols fro anti-HIV-1 gene therapy strategies is reviewed.

L5 ANSWER 10 OF 22 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:15336 CAPLUS
DOCUMENT NUMBER: 124:105329
TITLE: Development of in vivo gene therapy targeting hepatitis viral gene
AUTHOR(S): Yamada, Shuhei; Tanaka, Eiji
CORPORATE SOURCE: Fac. Med., Shinshu Univ., Matsumoto, 390, Japan
SOURCE: Igaku no Ayumi (1995), 175(9), 708-13
CODEN: IGAYAY; ISSN: 0039-2359
PUBLISHER: Ishiyaku
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A **review**, with 8 13 refs., on the technol. in **gene therapy** to exclusion of hepatitis virus by the methods of antisense, ribozyme, anti-viral proteins as RNA decoy, and induction of **cytotoxic T cells** (**CTL**) by expression of a part of the proteins of hepatitis virus. The current status of the study of gene therapy of hepatitis is discussed with the targets of hepatitis B virus (HBV) and gene cutter of hepatitis C virus (HCV).

L5 ANSWER 11 OF 22 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:15334 CAPLUS
DOCUMENT NUMBER: 124:105327
TITLE: Gene therapy of brain tumor with DNA/liposome
AUTHOR(S): Ohta, Seiji; Yoshida, Jun
CORPORATE SOURCE: Sch. Med., Nagoya Univ., Nagoya, 466, Japan
SOURCE: Igaku no Ayumi (1995), 175(9), 701-4
CODEN: IGAYAY; ISSN: 0039-2359
PUBLISHER: Ishiyaku
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A **review**, with 10 refs., on the poor prognosis of the current therapy of malignant glioma, and **gene therapy** of malignant glioma using cytokine gene harboring **cytotoxic T cells** (**CTL**), antisense gene, suicide gene, and cytokine **gene therapy** to glioma cells. Immunoliposome and plasmid are described for transfection of genes of interferon .gamma. or tumor necrosis factor .alpha. (TNF.alpha.) to glioma cells, and the exptl. results are discussed. The therapy leads to mol. neurosurgery.

L5 ANSWER 12 OF 22 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2003081197 EMBASE
TITLE: Prospects for CD40-directed experimental therapy of human cancer.
AUTHOR: Tong A.W.; Stone M.J.
CORPORATE SOURCE: Dr. A.W. Tong, Cancer Immunol. Research Laboratory, Baylor Sammons Cancer Center, 3500 Gaston Avenue, Dallas, TX 75246, United States. alext@baylorhealth.edu
SOURCE: Cancer Gene Therapy, (1 Jan 2003) 10/1 (1-13).
Refs: 155
ISSN: 0929-1903 CODEN: CGTHEG
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB CD40, a member of the tumor necrosis factor receptor (TNF-R) family, is a surface receptor best known for its capacity to initiate multifaceted activation signals in normal B cells and dendritic cells (DCs). CD40-related treatment approaches have been considered for the experimental therapy of human leukemias, lymphomas, and multiple myeloma, based on findings that CD40 binding by its natural ligand (CD40L), CD154, led to growth modulation of malignant B cells. Recent studies also exploited the selective expression of the CD40 receptor on human epithelial and mesenchymal tumors but not on most normal, nonproliferating epithelial tissues. Ligation of CD40 on human breast, ovarian, cervical, bladder, non small cell lung, and squamous epithelial carcinoma cells was found to produce a direct growth-inhibitory effect through cell cycle blockage and/or apoptotic induction with no overt side effects on their normal counterparts. CD154 treatment also heightened tumor rejection immune responses through DC activation, and by increasing tumor immunogenicity through up-regulation of costimulatory molecule expression and cytokine production of epithelial cancer cells. These immunopotentiating features can produce a "bystander effect" through which the CD40-negative tumor subset is eliminated by activated tumor-reactive **cytotoxic T cells**. However, the potential risk of systemic inflammation and autoimmune consequences remains a concern for systemic CD154-based experimental therapy. The promise of CD154 as a tumor therapeutic agent to directly modulate tumor cell growth, and indirectly activate antitumor immune response, may depend on selective and/or restricted CD154 expression within the tumor microenvironment. This may be achieved by inoculating cancer vaccines of autologous cancer cells that have been transduced ex vivo with CD154, as documented by recently clinical trials. This **review** summarizes recent findings on CD154 recombinant protein- and **gene therapy**-based tumor treatment approaches, and examines our understanding of the multifaceted

molecular mechanisms of CD154-CD40 interactions.

L5 ANSWER 13 OF 22 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001417879 EMBASE
TITLE: Pharmacotherapy by intracellular delivery of drugs using fusogenic liposomes: Application to vaccine development.
AUTHOR: Kunisawa J.; Nakagawa S.; Mayumi T.
CORPORATE SOURCE: T. Mayumi, Department of Biopharmaceutics, Grad. School of Pharmaceut. Sciences, Osaka University, 1-6 Yamadaoka, Osaka 565-0871, Japan. mayumi@phs.osaka-u.ac.jp
SOURCE: Advanced Drug Delivery Reviews, (19 Nov 2001) 52/3 (177-186).
Refs: 53
ISSN: 0169-409X CODEN: ADDREP
PUBLISHER IDENT.: S 0169-409X(01)00214-9
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
AB We prepared fusogenic liposomes by fusing conventional liposomes with an ultra-violet inactivated Sendai virus. Fusogenic liposomes can deliver encapsulated contents into the cytoplasm directly in a Sendai virus fusion-dependent manner. Based on the high delivery rates into the cytoplasm, we originally planned to apply the fusogenic liposomes to cancer chemotherapy and **gene therapy**. We have recently also examined the use of fusogenic liposomes as an antigen delivery vehicle. In terms of vaccine development, cytoplasmic delivery is crucial for the induction of the cytotoxic T lymphocyte (**CTL**) responses that play a pivotal role against infectious diseases and cancer. In this context, our recent studies suggested that fusogenic liposomes could deliver encapsulated antigens into the cytoplasm and induce MHC class I-restricted, antigen-specific **CTL** responses. In addition, fusogenic liposomes are also effective as a mucosal vaccine carrier. In this **review**, we present the feasibility of fusogenic liposomes as a versatile and effective antigen delivery system.

L5 ANSWER 14 OF 22 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001179587 EMBASE
TITLE: Chronic rejection.
AUTHOR: Libby P.; Pober J.S.
CORPORATE SOURCE: P. Libby, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA 02115, United States. plibby@rics.bwh.harvard.edu
SOURCE: Immunity, (2001) 14/4 (387-397).
Refs: 61
ISSN: 1074-7613 CODEN: IUNIEH
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 009 Surgery
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB In this **review**, we have suggested that chronic vascular rejection, defined as alloimmune-mediated graft vascular stenosis, is the primary cause of late cardiac and hepatic graft failure. It may also commonly contribute to late renal and pulmonary allograft loss. In contrast, parenchymal changes in these failing grafts likely reflect ischemia rather than chronic parenchymal cell rejection. Vascular stenosis results from a combination of intimal hyperplasia and constrictive remodeling. In chronic vascular rejection, as in other chronic vascular diseases (e.g., atherosclerosis), constrictive remodeling caused by adventitial cicatrix formation may be the more important contributor to lumen loss. Functional vascular dysregulation due to endothelial injury may exacerbate the degree of stenosis by promoting vasoconstriction. The precise immunological mechanisms that cause chronic vascular rejection are

unknown. Chronic DTH, mediated by host CD4(+) T cells activated by graft alloantigens that are presented directly by graft endothelial and dendritic cells or indirectly by host dendritic cells, is a likely candidate. Evidence that IFN-.gamma., the prototypic cytokine of DTH, is necessary and sufficient to cause vascular remodeling in experimental transplantation supports this concept. (Animal models have limitations in recreating the human disease, although they do provide insights into possible mechanisms.) Alternatively, low-level, smoldering acute vascular rejection mediated by CD8(+) **CTL** or alloantibodies could contribute to graft vascular disease. Nonimmunological factors, such as ischemia/reperfusion, hypertension, hyperlipidemia, and infection, all of which contribute to atherosclerotic vascular disease, all increase the incidence of chronic vascular rejection. These factors may act by enhancing the total burden of injury in the blood vessels or by activating the innate immune system, which favors the development of DTH. Human studies have not as yet resolved these issues. We currently lack effective preventive or therapeutic strategies for chronic vascular rejection. Current immunosuppressive regimens, which effectively prevent or abrogate acute rejection episodes, may target the wrong mechanisms; newer agents, such as rapamycin, may be more effective. Control of hypertension and restoration of normal lipid profiles, e.g., with HMG-CoA reductase inhibitors, may also be of benefit. In the future, as the pathogenesis is better understood, somatic **gene therapy** may provide a new avenue for therapy.

L5 ANSWER 15 OF 22 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001130994 EMBASE
TITLE: Gene-based cancer vaccines: An ex vivo approach.
AUTHOR: Van Tendeloo V.F.I.; Van Broeckhoven C.; Berneman Z.N.
CORPORATE SOURCE: Z.N. Berneman, Division of Hematology, Antwerp University Hospital, Wilrijkstraat 10, B-2650 Edegem, Belgium
SOURCE: Leukemia, (2001) 15/4 (545-558).
Refs: 196
ISSN: 0887-6924 CODEN: LEUKED
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
022 Human Genetics
026 Immunology, Serology and Transplantation
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The application of gene transfer techniques to immunotherapy has animated the field of gene-based cancer vaccine research. Gene transfer strategies were developed to bring about active immunization against tumor-associated antigens (TAA) through gene transfer technology. A wide variety of viral and nonviral gene transfer methods have been investigated for immunotherapeutic purposes. Ex vivo strategies include gene delivery into tumor cells and into cellular components of the immune system, including **cytotoxic T cells** and dendritic cells (DC).
The nature of the transferred genetic material as well as the gene transfer method has varied widely depending on the application. Several of these approaches have already been translated into clinical **gene therapy** trials. In this **review**, we will focus on the rationale and types of ex vivo gene-based immunotherapy of cancer. Critical areas for future development at gene-based cancer vaccines are addressed, with particular emphasis on use of DC and on the danger tolerance hypothesis. Finally, the use of gene-modified DC for tumor vaccination and its prospects are discussed.

L5 ANSWER 16 OF 22 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000011980 EMBASE
TITLE: Cell therapy: Achievements and perspectives.
AUTHOR: Bordignon C.; Carlo-Stella C.; Colombo M.P.; De Vincentiis A.; Lanata L.; Lemoli R.M.; Locatelli F.; Olivieri A.; Rondelli D.; Zanon P.; Tura S.
CORPORATE SOURCE: Prof. S. Tura, Ist. Ematologia Oncologia Seragnoli, Policlinico S. Orsola, Via Massarenti 9, 40138 Bologna, Italy. tura@orsola-malpighi.unibo.it

SOURCE: Haematologica, (1999) 84/12 (1110-1149).
Refs: 361
ISSN: 0390-6078 CODEN: HAEMAX
COUNTRY: Italy
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 025 Hematology
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Background and Objectives. Cell therapy can be considered as a strategy aimed at replacing, repairing, or enhancing the biological function of a damaged tissue or system by means of autologous or allogeneic cells. There have been major advances in this field in the last few years. This has prompted the Working Group on Hematopoietic Cells to examine the current utilization of this therapy in clinical hematology. Evidence and Information Sources. The method employed for preparing this **review** was that of informal consensus development. Members of the Working Group met three times, and the participants at these meetings examined a list of problems previously prepared by the chairman. They discussed the single points in order to reach an agreement on different opinions and eventually approved the final manuscript. Some of the authors of the present **review** have been working in the field of cell therapy and have contributed original papers in peer- reviewed journals. In addition, the material examined in the present **review** includes articles and abstracts published in journals covered by the Science Citation Index and Medline. State of the Art. Lymphokine-activated killer (LAK) and tumor-infiltrating lymphocytes (TIL) have been used since the '70s mainly in end-stage patients with solid tumors, but the clinical benefits of these treatments has not been clearly documented. TIL are more specific and potent cytotoxic effectors than LAK, but only in few patients (mainly in those with solid tumors such as melanoma and glioblastoma) can their clinical use be considered potentially useful. Adoptive immunotherapy with donor lymphocyte infusions has proved to be effective, particularly in patients with chronic myeloid leukemia, in restoring a state of hematologic remission after leukemia relapse occurring following an allograft. The infusion of donor T-cells can also have a role in the treatment of patients with Epstein- Barr virus (EBV)-induced post-transplant lymphoproliferative disorders. However, in this regard, generation and infusion of donor-derived, virus specific T-cell lines or clones represents a more sophisticated and safer approach for treatment of viral complications occurring in immunocompromized patients. Whereas too few clinical trials have been performed so far to draw any firm conclusion, based on animal studies dendritic cell-based immunotherapy holds promises of exerting an effective anti-tumor activity. Despite leukemic cells not being immunogenic, induction on their surface of co-stimulatory molecules or generation of leukemic dendritic cells may induce antileukemic **cytotoxic T-cell** responses. Tumor cells express a variety of antigens and can be genetically manipulated to become immunogenic. The main in vitro and in vivo functional characteristics of marrow mesenchymal stem cells (MSCs) with particular emphasis on their hematopoietic regulatory role are reviewed. In addition, prerequisites for clinical applications using culture-expanded mesenchymal cells are discussed perspectives. The opportuneness of using LAK cells or activated natural killer (NK) cells in hematologic patients with low tumor burden (e.g. after stem cell transplantation) should be further explored. Moreover the role of new cytokines in enhancing the antineoplastic activity of NK cells and the infusion of selected NK in alternative to **CTL** for graft versus leukemia (GVL) disease (avoiding graft versus host disease (GvHD) seems very promising. Separation of GVL from GvHD through generation and infusion of leukemia- specific T-cell clones or lines is one of the most intriguing and promising fields of investigations for the future, likewise, strategies devised to improve immune-reconstitution and restore specific anti-infectious functions through either induction of unresponsiveness to recipient alloantigens or removal of alloreactive donor T-cells might increase the applicability and success of hematopoietic stem cell transplantation. Cellular immunotherapy with DC must be standardized and several critical points, discussed in the chapter, have to be properly addressed with specific clinical studies. Stimulation of leukemic cells via CD40 receptor and transduction of tumor

cells with co-stimulatory molecules and/or cytokines may be useful to prevent a tumor escaping immune surveillance. Tumor cells can be genetically modified to interact directly with dendritic cells in vivo or recombinant antigen can be delivered to dendritic cells using attenuated bacterial vectors for oral vaccination. MSCs represent an attractive therapeutic tool capable of playing a role in a wide range of clinical applications in the context of both cell and **gene therapy** strategies.

L5 ANSWER 17 OF 22 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 96162508 EMBASE
DOCUMENT NUMBER: 1996162508
TITLE: Gene therapy for HIV infection.
AUTHOR: Bunnell B.A.; Morgan R.A.
CORPORATE SOURCE: Clinical Gene Therapy Branch, Nat. Center Human Genome Research, National Institutes of Health,Bethesda, MD 20892, United States
SOURCE: Drugs of Today, (1996) 32/3 (209-224).
ISSN: 0025-7656 CODEN: MDACAP
COUNTRY: Spain
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The ultimate goal of **gene therapy** for HIV-1 is to inhibit viral replication and the resultant AIDS pathogenesis. **Gene therapy** for HIV-1 requires the introduction of genes that effectively inhibit viral replication by blocking expression of viral genes or altering the normal function of HIV-1 associated proteins. This **review** details the various anti-HIV-1 **gene therapy** strategies that have been developed to effectively inhibit HIV-1 replication. The **review** covers three broad categories: i) **gene therapy** using nucleic acid moieties such as gene vaccines, antisense DNA/RNA, RNA decoys, and ribozymes; ii) protein approaches such as trans-dominant negative proteins and single chain antibodies; and iii) immunotherapy using HIV-1 specific **cytotoxic T cells**. The discussion focuses on the effectiveness of the various techniques in preclinical experiments and in animal models. Also, the status of all of the current RAC/FDA approved clinical protocols for anti-HIV-1 **gene therapy** strategies is reviewed.

L5 ANSWER 18 OF 22 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94032629 EMBASE
DOCUMENT NUMBER: 1994032629
TITLE: Somatic gene therapy for cancer: The utility of transferrinfection in generating 'tumor vaccines'.
AUTHOR: Zatloukal K.; Schmidt W.; Cotten M.; Wagner E.; Stingl G.; Birnstiel M.L.
CORPORATE SOURCE: Molecular Pathology Research Inst., Dr. Bohr-Gasse 7,A-1030 Vienna, Austria
SOURCE: Gene, (1993) 135/1-2 (199-207).
ISSN: 0378-1119 CODEN: GENED6
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
022 Human Genetics
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The last few years have seen the development of a branch of somatic **gene therapy** which aims at strengthening the immune surveillance of the body, leading to eradication of disseminated cancer tumor cells and occult micrometastases after surgical removal of the primary tumor. Such a tumor vaccination protocol calls for cultivation of the primary tumor tissue and the insertion of one of three types of genes into the isolated cultured tumor cells followed by irradiation of the transfected or transduced cells to render them incapable of further

proliferation. The cells so treated constitute the 'tumor vaccine'. A **review** of the literature suggests that for mouse models, in the initial period after inoculation, rejection of the tumor cells is usually effected by non-T-cell immunity, whereas the long-term systemic immune response is based on **cytotoxic T-cells**. High expression of the gene inserted into the tumor cells may be critical for the success of the vaccination procedure. Examples are given which indicate that transferrinfection, a procedure to introduce genes by adenovirus-augmented receptor-mediated endocytosis, meets some important prerequisites for successful application of this type of **gene therapy**.

L5 ANSWER 19 OF 22 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2003:138397 BIOSIS
DOCUMENT NUMBER: PREV200300138397
TITLE: Prospects for CD40-directed experimental therapy of human cancer.
AUTHOR(S): Tong, Alex W. (1); Stone, Marvin J.
CORPORATE SOURCE: (1) Cancer Immunology Research Laboratory, Baylor Sammons Cancer Center, 3500 Gaston Avenue, Dallas, TX, 75246, USA: alext@baylorhealth.edu USA
SOURCE: Cancer Gene Therapy, (January 2003, 2003) Vol. 10, No. 1, pp. 1-13. print.
ISSN: 0929-1903.
DOCUMENT TYPE: General Review
LANGUAGE: English
AB CD40, a member of the tumor necrosis factor receptor (TNF-R) family, is a surface receptor best known for its capacity to initiate multifaceted activation signals in normal B cells and dendritic cells (DCs). CD40-related treatment approaches have been considered for the experimental therapy of human leukemias, lymphomas, and multiple myeloma, based on findings that CD40 binding by its natural ligand (CD40L), CD154, led to growth modulation of malignant B cells. Recent studies also exploited the selective expression of the CD40 receptor on human epithelial and mesenchymal tumors but not on most normal, nonproliferating epithelial tissues. Ligation of CD40 on human breast, ovarian, cervical, bladder, non small cell lung, and squamous epithelial carcinoma cells was found to produce a direct growth-inhibitory effect through cell cycle blockage and/or apoptotic induction with no overt side effects on their normal counterparts. CD154 treatment also heightened tumor rejection immune responses through DC activation, and by increasing tumor immunogenicity through up-regulation of costimulatory molecule expression and cytokine production of epithelial cancer cells. These immunopotentiating features can produce a "bystander effect" through which the CD40-negative tumor subset is eliminated by activated tumor-reactive **cytotoxic T cells**. However, the potential risk of systemic inflammation and autoimmune consequences remains a concern for systemic CD154-based experimental therapy. The promise of CD154 as a tumor therapeutic agent to directly modulate tumor cell growth, and indirectly activate antitumor immune response, may depend on selective and/or restricted CD154 expression within the tumor microenvironment. This may be achieved by inoculating cancer vaccines of autologous cancer cells that have been transduced ex vivo with CD154, as documented by recently clinical trials. This **review** summarizes recent findings on CD154 recombinant protein- and **gene therapy**-based tumor treatment approaches, and examines our understanding of the multifaceted molecular mechanisms of CD154-CD40 interactions.

L5 ANSWER 20 OF 22 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:237077 BIOSIS
DOCUMENT NUMBER: PREV200100237077
TITLE: Gene-based cancer vaccines: An ex vivo approach.
AUTHOR(S): Van Tendeloo, V. F. I.; Van Broeckhoven, C.; Berneman, Z. N. (1)
CORPORATE SOURCE: (1) Division of Hematology, Antwerp University Hospital (UIA/UZA), Wilrijkstraat 10, B-2650, Edegem Belgium
SOURCE: Leukemia (Basingstoke), (April, 2001) Vol. 15, No. 4, pp. 545-558. print.
ISSN: 0887-6924.
DOCUMENT TYPE: General Review

LANGUAGE: English
SUMMARY LANGUAGE: English
AB The application of gene transfer techniques to immunotherapy has animated the field of gene-based cancer vaccine research. Gene transfer strategies were developed to bring about active immunization against tumor-associated antigens (TAA) through gene transfer technology. A wide variety of viral and nonviral gene transfer methods have been investigated for immunotherapeutic purposes. Ex vivo strategies include gene delivery into tumor cells and into cellular components of the immune system, including **cytotoxic T cells** and dendritic cells (DC).
The nature of the transferred genetic material as well as the gene transfer method has varied widely depending on the application. Several of these approaches have already been translated into clinical **gene therapy** trials. In this **review**, we will focus on the rationale and types of ex vivo gene-based immunotherapy of cancer. Critical areas for future development of gene-based cancer vaccines are addressed, with particular emphasis on use of DC and on the danger-tolerance hypothesis. Finally, the use of gene-modified DC for tumor vaccination and its prospects are discussed.

L5 ANSWER 21 OF 22 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:121603 BIOSIS
DOCUMENT NUMBER: PREV200000121603
TITLE: Cell therapy: Achievements and perspectives.
AUTHOR(S): Bordignon, Claudio; Carlo-Stella, Carmelo; Colombo, Mario Paolo; De Vincentiis, Armando; Lanata, Luigi; Massimo Lemoli, Roberto; Locatelli, Franco; Olivieri, Attilio; Rondelli, Damiano; Zanon, Paola; Tura, Sante (1)
CORPORATE SOURCE: (1) Istituto di Ematologia e Oncologia Seragnoli, Policlinico S. Orsola, Via Massarenti 9, 40138, Bologna Italy
SOURCE: Haematologica, (Dec., 1999) Vol. 84, No. 12, pp. 1110-1149. ISSN: 0390-6078.
DOCUMENT TYPE: General Review
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Background and Objectives: Cell therapy can be considered as a strategy aimed at replacing, repairing, or enhancing the biological function of a damaged tissue or system by means of autologous or allogeneic cells. There have been major advances in this field in the last few years. This has prompted the Working Group on Hematopoietic Cells to examine the current utilization of this therapy in clinical hematology. Evidence and Information Sources: The method employed for preparing this **review** was that of informal consensus development. Members of the Working Group met three times, and the participants at these meetings examined a list of problems previously prepared by the chairman. They discussed the single points in order to reach an agreement on different opinions and eventually approved the final manuscript. Some of the authors of the present **review** have been working in the field of cell therapy and have contributed original papers in peer-reviewed journals. In addition, the material examined in the present **review** includes articles and abstracts published in journals covered by the Science Citation Index and Medline. State of the Art: Lymphokine-activated killer (LAK) and tumor-infiltrating lymphocytes (TIL) have been used since the '70s mainly in end-stage patients with solid tumors, but the clinical benefits of these treatments has not been clearly documented. TIL are more specific and potent cytotoxic effectors than LAK, but only in few patients (mainly in those with solid tumors such as mélanoma and glioblastoma) can their clinical use be considered potentially useful. Adoptive immunotherapy with donor lymphocyte infusions has proved to be effective, particularly in patients with chronic myeloid leukemia, in restoring a state of hematologic remission after leukemia relapse occurring following an allograft. The infusion of donor T-cells can also have a role in the treatment of patients with Epstein-Barr virus (EBV)-induced post-transplant lymphoproliferative disorders. However, in this regard, generation and infusion of donor-derived, virus specific T-cell lines or clones represents a more sophisticated and safer approach for treatment of viral complications occurring in immunocompromized patients. Whereas too few clinical trials have been performed so far to draw any firm conclusion, based on animal studies dendritic cell-based immunotherapy

holds promises of exerting an effective anti-tumor activity. Despite leukemic cells not being immunogenic, induction on their surface of co-stimulatory molecules or generation of leukemic dendritic cells may induce antileukemic **cytotoxic T-cell** responses. Tumor cells express a variety of antigens and can be genetically manipulated to become immunogenic. The main in vitro and in vivo functional characteristics of marrow mesenchymal stem cells (MSCs) with particular emphasis on their hematopoietic regulatory role are reviewed. In addition, prerequisites for clinical applications using culture-expanded mesenchymal cells are discussed Perspectives: The opportuneness of using LAK cells or activated natural killer (NK) cells in hematologic patients with low tumor burden (e.g. after stem cell transplantation) should be further explored. Moreover the role of new cytokines in enhancing the antineoplastic activity of NK cells and the infusion of selected NK in alternative to **CTL** for graft versus leukemia (GVL) disease (avoiding graft versus host disease (GvHD) seems very promising. Separation of GVL from GvHD through generation and infusion of leukemia-specific T-cell clones or lines is one of the most intriguing and promising fields of investigations for the future. Likewise, strategies devised to improve immune-reconstitution and restore specific anti-infectious functions through either induction of unresponsiveness to recipient alloantigens or removal of alloreactive donor T-cells might increase the applicability and success of hematopoietic stem cell transplantation. Cellular immunotherapy with DC must be standardized and several critical points, discussed in the chapter, have to be properly addressed with specific clinical studies. Stimulation of leukemic cells via CD40 receptor and transduction of tumor cells with co-stimulatory molecules and/or cytokines may be useful to prevent a tumor escaping immune surveillance. Tumor cells can be genetically modified to interact directly with dendritic cells in vivo or recombinant antigen can be delivered to dendritic cells using attenuated bacterial vectors for oral vaccination. MSCs represent an attractive therapeutic tool capable of playing a role in a wide range of clinical applications in the context of both cell and **gene therapy** strategies.

L5 ANSWER 22 OF 22 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1994:130537 BIOSIS
DOCUMENT NUMBER: PREV199497143537
TITLE: Somatic gene therapy for cancer: The utility of transferrinfection in generating 'tumor vaccines.
AUTHOR(S): Zatloukal, Kurt; Schmidt, Walter; Cotten, Matthew; Wagner, Ernest; Stingl, Georg; Birnstiel, Max L. (1)
CORPORATE SOURCE: (1) Research Inst. Molecular Pathol., Dr. Bohr-Gasse 7, A-1030 Vienna Austria
SOURCE: Gene (Amsterdam), (1993) Vol. 135, No. 1-2, pp. 199-207. ISSN: 0378-1119.
DOCUMENT TYPE: Article
LANGUAGE: English

AB The last few years have seen the development of a branch of somatic **gene therapy** which aims at strengthening the immune surveillance of the body, leading to eradication of disseminated cancer tumor cells and occult micrometastases after surgical removal of the primary tumor. Such a tumor vaccination protocol calls for cultivation of the primary tumor tissue and the insertion of one of three types of genes into the isolated cultured tumor cells followed by irradiation of the transfected or transduced cells to render them incapable of further proliferation. The cells so treated constitute the 'tumor vaccine'. A **review** of the literature suggests that for mouse models, in the initial period after inoculation, rejection of the tumor cells is usually effected by non-T-cell immunity, whereas the long-term systemic immune response is based on **cytotoxic T-cells**. High expression of the gene inserted into the tumor cells may be critical for the success of the vaccination procedure. Examples are given which indicate that transferrinfection, a procedure to introduce genes by adenovirus-augmented receptor-mediated endocytosis, meets some important prerequisites for successful application of this type of **gene therapy**.

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=> d his

     (FILE 'HOME' ENTERED AT 09:29:48 ON 18 MAR 2003)

     FILE 'MEDLINE, CAPLUS, EMBASE, BIOSIS' ENTERED AT 09:30:09 ON 18 MAR 2003
L1         88979 S GENE THERAPY
L2       3193730 S REVIEW
L3         54069 S CTL OR CYTOTOXIC T CELLS
L4         61025 S CTL OR CYTOTOXIC T CELL?
L5            22 S L1 (S) L2 (S) L3 (S) L4

=> s granzyme? inhibitor or serpin or p19 or sp16
L6         13258 GRANZYME? INHIBITOR OR SERPIN OR P19 OR SP16

=> s l1 (S) l2 (S) l3 (S) l4 (S) l6
L7             0 L1 (S) L2 (S) L3 (S) L4 (S) L6

=> s l1 (l) l2 (l) l3 (l) l4 (l) l6
L8             0 L1 (L) L2 (L) L3 (L) L4 (L) L6

=> s l1 (S) l3 (S) l4 (S) l6
L9             0 L1 (S) L3 (S) L4 (S) L6

=> s l1 (S) l4 (S) l6
L10            0 L1 (S) L4 (S) L6

=> s l1 (l) l4 (l) l6
L11            0 L1 (L) L4 (L) L6

=> s l1 (l) l6
L12           62 L1 (L) L6

=> s l12 and l3
L13            0 L12 AND L3

=> s l1 (s) l6
L14           49 L1 (S) L6

=> s l1 (s) l6 (S) l2
L15            0 L1 (S) L6 (S) L2

=> s l1 (l) l6 (l) l2
L16            2 L1 (L) L6 (L) L2

=> d 1-2 ibib abs

L16  ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2002:936128  CAPLUS
TITLE:                    Antiangiogenic gene therapy
AUTHOR(S):                Cao, Yihai
CORPORATE SOURCE:         Laboratory of Angiogenesis Research, Microbiology and
                          Tumor Biology Center, Karolinska Institute, Stockholm,
                          S-17177, Swed.
SOURCE:                   Gene Therapy and Regulation (2000), 1(2), 123-139
                          CODEN: GTREBR; ISSN: 1388-9532
PUBLISHER:                VSP BV
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   A no. of potent endogenous inhibitors targeting the tumor vasculature have
     recently been identified in tumor-bearing animals.  Some of these
     angiogenesis inhibitors, including angiostatin, endostatin, and
     serpin antithrombin, seem to act specifically on the proliferating
     endothelial cells in the newly formed blood vessels.  The discovery of
     these specific endothelial inhibitors not only increases our understanding
     of the functions of these mols. in the regulation of physiol. and pathol.
     angiogenesis, but also provides an important therapeutic strategy for
     cancer treatment.  Several studies have demonstrated that antiangiogenic
     protein therapy with these inhibitors significantly suppresses the growth
     of a variety of tumors in mice.  However, the dosages of these endogenous
     inhibitors used in animal studies seem to be too high for clin. trials.
```

Other disadvantages of antiangiogenic protein therapy include repeated injections, prolonged treatment, potential transmission of toxins and infectious particles, and high cost for manufg. large amts. of protein mols. Thus, alternative approaches need to be developed in order to improve the antiangiogenic therapy with endogenous inhibitors. Perhaps **gene therapy** aimed to express these potent angiogenesis inhibitors in vivo is the most promising alternative approach that could transfer antiangiogenic therapy from animal expts. into the clinic. Although the development of this field is still in its early stages, several studies in animals have already provided evidence that this is a promising approach in the treatment of cancer. In this **review** article, I will discuss the therapeutic potentials of antiangiogenic mols. expressed from **gene therapy** vectors.

REFERENCE COUNT: 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:275346 CAPLUS
DOCUMENT NUMBER: 135:101790
TITLE: Endogenous angiogenesis inhibitors and their therapeutic implications
AUTHOR(S): Cao, Y.
CORPORATE SOURCE: Microbiology and Tumor Biology Center, Laboratory of Angiogenesis Research, Karolinska Institute, Stockholm, S-171 77, Swed.
SOURCE: International Journal of Biochemistry & Cell Biology (2001), 33(4), 357-369
CODEN: IJBBFU; ISSN: 1357-2725
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A **review** with 88 refs. A no. of endogenous inhibitors targeting the tumor vasculature have recently been identified using in vitro and in vivo antiangiogenesis models. While many of these angiogenesis inhibitors display a broad spectrum of biol. actions on several systems in the body, several inhibitors including angiostatin, endostatin, and **serpin** antithrombin seem to act specifically on the proliferating endothelial cell compartment of the newly formed blood vessels. The discovery of these specific endothelial inhibitors not only increases our understanding of the functions of these mols. in the regulation of physiol. and pathol. angiogenesis, but may also provide an important therapeutic strategy for the treatment of cancer and other angiogenesis dependent diseases, including diabetic retinopathy and chronic inflammations. Systemic administration of these angiogenesis inhibitors in animals significantly suppresses the growth of a variety of tumors and their metastases. However, their prodn. as functional recombinant proteins has been proven to be difficult. In addn., high dosages of these inhibitors are required to suppress tumor growth in animal studies. Other disadvantages of the antiangiogenic protein therapy include repeated injections, prolonged treatment, transmission of toxins and infectious particles, and high cost for manufg. large amts. of protein mols. Thus, alternative strategies need to be developed in order to improve the clin. settings of antiangiogenic therapy. Developments of these strategies are ongoing and they include identification of more potent inhibitors, antiangiogenic **gene therapy**, improvement of protein/compd. half-lives in the circulation, increase of their concns. at the disease location, and combinatorial therapies with approaches including chemotherapy, radiotherapy, and immunotherapy. Despite the above-mentioned disadvantages, a few inhibitors have entered into the early stages of clin. trials and they may bring new hopes for the treatment of cancer and other angiogenesis dependent diseases.

REFERENCE COUNT: 88 THERE ARE 88 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d hsi
'HSI' IS NOT A VALID FORMAT FOR FILE 'CAPLUS'

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ABS --------- GI and AB
ALL --------- BIB, AB, IND, RE
APPS -------- AI, PRAI
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CBIB -------- AN, plus Compressed Bibliographic Data
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DMAX -------- MAX, delimited for post-processing
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FBIB -------- AN, BIB, plus Patent FAM
IND --------- Indexing data
IPC --------- International Patent Classifications
MAX --------- ALL, plus Patent FAM, RE
PATS -------- PI, SO
SAM --------- CC, SX, TI, ST, IT
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IBIB -------- BIB, indented with text labels
IMAX -------- MAX, indented with text labels
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SBIB -------- BIB, no citations
SIBIB ------- IBIB, no citations

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              its structure diagram
HITSEQ ------ HIT RN, its text modification, its CA index name, its
              structure diagram, plus NTE and SEQ fields
FHITSTR ----- First HIT RN, its text modification, its CA index name, and
              its structure diagram
FHITSEQ ----- First HIT RN, its text modification, its CA index name, its
              structure diagram, plus NTE and SEQ fields
KWIC -------- Hit term plus 20 words on either side
OCC --------- Number of occurrence of hit term and field in which it occurs

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to view a specified Accession Number.
ENTER DISPLAY FORMAT (BIB):end

=> d his

     (FILE 'HOME' ENTERED AT 09:29:48 ON 18 MAR 2003)

     FILE 'MEDLINE, CAPLUS, EMBASE, BIOSIS' ENTERED AT 09:30:09 ON 18 MAR 2003
L1         88979 S GENE THERAPY
L2       3193730 S REVIEW
L3         54069 S CTL OR CYTOTOXIC T CELLS
L4         61025 S CTL OR CYTOTOXIC T CELL?
L5            22 S L1 (S) L2 (S) L3 (S) L4
L6         13258 S GRANZYME? INHIBITOR OR SERPIN OR P19 OR SP16
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L7            0 S L1 (S) L2 (S) L3 (S) L4 (S) L6
L8            0 S L1 (L) L2 (L) L3 (L) L4 (L) L6
L9            0 S L1 (S) L3 (S) L4 (S) L6
L10           0 S L1 (S) L4 (S) L6
L11           0 S L1 (L) L4 (L) L6
L12          62 S L1 (L) L6
L13           0 S L12 AND L3
L14          49 S L1 (S) L6
L15           0 S L1 (S) L6 (S) L2
L16           2 S L1 (L) L6 (L) L2

=> d l14 1-49 ibib abs

L14  ANSWER 1 OF 49     MEDLINE
ACCESSION NUMBER:   2002245761     MEDLINE
DOCUMENT NUMBER:    21980630   PubMed ID: 11972060
TITLE:              RNA interference by expression of short-interfering RNAs
                    and hairpin RNAs in mammalian cells.
AUTHOR:             Yu Jenn-Yah; DeRuiter Stacy L; Turner David L
CORPORATE SOURCE:   Mental Health Research Institute, Program in Neuroscience,
                    and Department of Biological Chemistry, University of
                    Michigan, Ann Arbor, MI 48109-0669, USA.
CONTRACT NUMBER:    NS38698 (NINDS)
SOURCE:             PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE
                    UNITED STATES OF AMERICA, (2002 Apr 30) 99 (9) 6047-52.
                    Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200206
ENTRY DATE:         Entered STN: 20020502
                    Last Updated on STN: 20030105
                    Entered Medline: 20020611
AB   Duplexes of 21-nt RNAs, known as short-interfering RNAs (siRNAs),
     efficiently inhibit gene expression by RNA interference (RNAi) when
     introduced into mammalian cells. We show that siRNAs can be synthesized by
     in vitro transcription with T7 RNA polymerase, providing an economical
     alternative to chemical synthesis of siRNAs. By using this method, we show
     that short hairpin siRNAs can function like siRNA duplexes to inhibit gene
     expression in a sequence-specific manner. Further, we find that hairpin
     siRNAs or siRNAs expressed from an RNA polymerase III vector based on the
     mouse U6 RNA promoter can effectively inhibit gene expression in mammalian
     cells. U6-driven hairpin siRNAs dramatically reduced the expression of a
     neuron-specific beta-tubulin protein during the neuronal differentiation
     of mouse P19 cells, demonstrating that this approach should be
     useful for studies of differentiation and neurogenesis. We also observe
     that mismatches within hairpin siRNAs can increase the strand selectivity
     of a hairpin siRNA, which may reduce self-targeting of vectors expressing
     siRNAs. Use of hairpin siRNA expression vectors for RNAi should provide a
     rapid and versatile method for assessing gene function in mammalian cells,
     and may have applications in gene therapy.

L14  ANSWER 2 OF 49     MEDLINE
ACCESSION NUMBER:   2002211468     MEDLINE
DOCUMENT NUMBER:    21945809   PubMed ID: 11945068
TITLE:              Functional evidence of CFTR gene transfer in nasal
                    epithelium of cystic fibrosis mice in vivo following
                    luminal application of DNA complexes targeted to the
                    serpin-enzyme complex receptor.
AUTHOR:             Ziady Assem-Galal; Kelley Thomas J; Milliken Erin; Ferkol
                    Thomas; Davis Pamela B
CORPORATE SOURCE:   Department of Pediatrics at Rainbow Babies and Childrens
                    Hospital, Case Western Reserve University School of
                    Medicine, Cleveland, Ohio 44106, USA.
CONTRACT NUMBER:    P30 DK27651 (NIDDK)
     RO1 58318
     RO1 DK52981 (NIDDK)
     T32 HL07415 (NHLBI)
SOURCE:             MOLECULAR THERAPY, (2002 Apr) 5 (4) 413-9.
```

Journal code: 100890581. ISSN: 1525-0016.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 20020412
Last Updated on STN: 20020928
Entered Medline: 20020927

AB Molecular conjugates that target the **serpin**-enzyme complex receptor transfer the cDNA encoding human cystic fibrosis transmembrane conductance regulator (CFTR) to the nasal epithelium of cystic fibrosis mutant mice. These complexes effect partial correction of the chloride transport defect as assessed by in vivo nasal potential difference measurements, produce immunohistochemical staining for CFTR, and restore expression of nitric oxide synthase-2 (NOS-2), which is downregulated in the epithelium of mice and humans with cystic fibrosis. Complexes that lack the receptor ligands were ineffective, so receptor access was essential. Mice treated with receptor-targeted lacZ showed beta-galactosidase expression in epithelial cells and submucosal glands, but no electrophysiologic correction or NOS-2 expression, so simply accessing the **serpin**-enzyme complex receptor was not sufficient to produce the observed electrophysiologic or immunohistochemical changes. Correction of the cAMP-stimulated chloride transport was dose related at days 7 and 12 after complex administration, but, for most animals, nasal potential difference had returned to baseline by day 18. Molecular conjugates targeting the **serpin**-enzyme complex receptor, used to compact plasmid DNA, hold promise for **gene therapy** of cystic fibrosis.

L14 ANSWER 3 OF 49 MEDLINE
ACCESSION NUMBER: 2001464622 MEDLINE
DOCUMENT NUMBER: 21400689 PubMed ID: 11509889
TITLE: Characterization of permanent cell lines that contain the AAV2 rep-cap genes on an Epstein-Barr-virus-based episomal plasmid.
AUTHOR: Neyns B; Vermeij J; Teugels E; De Rijcke M; Hermonat P; De Greve J
CORPORATE SOURCE: Laboratory of Medical Oncology, Oncologisch Centrum, Akademisch Ziekenhuis, Vrije Universiteit Brussel, Laarbeeklaan 101, B-1090 Brussels, Belgium.
SOURCE: INTERVIROLOGY, (2001) 44 (4) 255-63.
Journal code: 0364265. ISSN: 0300-5526.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20010820
Last Updated on STN: 20011015
Entered Medline: 20011011

AB Recombinant adeno-associated virus (rAAV) has emerged as a promising **gene therapy** vector. Its development, however, has been hampered by the lack of a readily available efficient production method. We investigated the possibility of establishing permanent cell lines for the production of rAAV with a new Epstein-Barr-virus (EBV)-based episomal AAV rep-cap plasmid (pCEP-rep/cap). HeLa and 293 cells were stably transfected with plasmids that carry the AAV2 rep/cap genes under transcriptional control of their endogenous promoters (p5, **p19** and p40) either on the pCEP-rep/cap or an integrated (pIM45) plasmid. For the ease of monitoring transgene expression in live cells, a rAAV vector expressing gfp (the green fluorescent protein gene, rAAV-gfp/neo) was used. Establishment of stable transfected cell lines with these plasmids proved feasible but their usefulness was limited because of their instability. Within 8-12 weeks after their establishment, stably transfected rep-cap cell lines invariably lost their function. In addition, the rAAV-gfp/neo vector we used was susceptible to mutation in stably transfected HeLa cells. Our observations demonstrate specific problems both at the level of rep/cap gene function and the rAAV genome that can occur with the establishment of rAAV production cell lines. These

experiments should aid the further development of efficient rAAV production protocols.

L14 ANSWER 4 OF 49 MEDLINE
ACCESSION NUMBER: 2001222590 MEDLINE
DOCUMENT NUMBER: 21212046 PubMed ID: 11312106
TITLE: Endogenous angiogenesis inhibitors and their therapeutic implications.
AUTHOR: Cao Y
CORPORATE SOURCE: Laboratory of Angiogenesis Research, Microbiology and Tumor Biology Center, Karolinska Institute, S-171 77, Stockholm, Sweden.. yihai.cao@mtc.ki.se
SOURCE: INTERNATIONAL JOURNAL OF BIOCHEMISTRY AND CELL BIOLOGY, (2001 Apr) 33 (4) 357-69. Ref: 88
Journal code: 9508482. ISSN: 1357-2725.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010625
Last Updated on STN: 20010625
Entered Medline: 20010621

AB A number of endogenous inhibitors targeting the tumor vasculature have recently been identified using in vitro and in vivo antiangiogenesis models. While many of these angiogenesis inhibitors display a broad spectrum of biological actions on several systems in the body, several inhibitors including angiostatin, endostatin, and **serpin** antithrombin seem to act specifically on the proliferating endothelial cell compartment of the newly formed blood vessels. The discovery of these specific endothelial inhibitors not only increases our understanding of the functions of these molecules in the regulation of physiological and pathological angiogenesis, but may also provide an important therapeutic strategy for the treatment of cancer and other angiogenesis dependent diseases, including diabetic retinopathy and chronic inflammations. Systemic administration of these angiogenesis inhibitors in animals significantly suppresses the growth of a variety of tumors and their metastases. However, their production as functional recombinant proteins has been proven to be difficult. In addition, high dosages of these inhibitors are required to suppress tumor growth in animal studies. Other disadvantages of the antiangiogenic protein therapy include repeated injections, prolonged treatment, transmission of toxins and infectious particles, and high cost for manufacturing large amounts of protein molecules. Thus, alternative strategies need to be developed in order to improve the clinical settings of antiangiogenic therapy. Developments of these strategies are ongoing and they include identification of more potent inhibitors, antiangiogenic **gene therapy**, improvement of protein/compound half-lives in the circulation, increase of their concentrations at the disease location, and combinatorial therapies with approaches including chemotherapy, radiotherapy, and immunotherapy. Despite the above-mentioned disadvantages, a few inhibitors have entered into the early stages of clinical trials and they may bring new hopes for the treatment of cancer and other angiogenesis dependent diseases.

L14 ANSWER 5 OF 49 MEDLINE
ACCESSION NUMBER: 2000459418 MEDLINE
DOCUMENT NUMBER: 20411438 PubMed ID: 10954565
TITLE: Mutational analysis of the adeno-associated virus type 2 (AAV2) capsid gene and construction of AAV2 vectors with altered tropism.
AUTHOR: Wu P; Xiao W; Conlon T; Hughes J; Agbandje-McKenna M; Ferkol T; Flotte T; Muzyczka N
CORPORATE SOURCE: Department of Molecular Genetics and Microbiology, University of Florida, Gainesville, Florida 32610-0266, USA.
CONTRACT NUMBER: PO1 HL51811 (NHLBI)
PO1 HL59412 (NHLBI)

PO1 NS36302 (NINDS)
SOURCE: JOURNAL OF VIROLOGY, (2000 Sep) 74 (18) 8635-47.
Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20001005
Last Updated on STN: 20001005
Entered Medline: 20000927

AB Adeno-associated virus type 2 (AAV2) has proven to be a valuable vector for **gene therapy**. Characterization of the functional domains of the AAV capsid proteins can facilitate our understanding of viral tissue tropism, immunoreactivity, viral entry, and DNA packaging, all of which are important issues for generating improved vectors. To obtain a comprehensive genetic map of the AAV capsid gene, we have constructed 93 mutants at 59 different positions in the AAV capsid gene by site-directed mutagenesis. Several types of mutants were studied, including epitope tag or ligand insertion mutants, alanine scanning mutants, and epitope substitution mutants. Analysis of these mutants revealed eight separate phenotypes. Infectious titers of the mutants revealed four classes. Class 1 mutants were viable, class 2 mutants were partially defective, class 3 mutants were temperature sensitive, and class 4 mutants were noninfectious. Further analysis revealed some of the defects in the class 2, 3, and 4 mutants. Among the class 4 mutants, a subset completely abolished capsid formation. These mutants were located predominantly, but not exclusively, in what are likely to be beta-barrel structures in the capsid protein VP3. Two of these mutants were insertions at the N and C termini of VP3, suggesting that both ends of VP3 play a role that is important for capsid assembly or stability. Several class 2 and 3 mutants produced capsids that were unstable during purification of viral particles. One mutant, R432A, made only empty capsids, presumably due to a defect in packaging viral DNA. Additionally, five mutants were defective in heparan binding, a step that is believed to be essential for viral entry. These were distributed into two amino acid clusters in what is likely to be a cell surface loop in the capsid protein VP3. The first cluster spanned amino acids 509 to 522; the second was between amino acids 561 and 591. In addition to the heparan binding clusters, hemagglutinin epitope tag insertions identified several other regions that were on the surface of the capsid. These included insertions at amino acids 1, 34, 138, 266, 447, 591, and 664. Positions 1 and 138 were the N termini of VP1 and VP2, respectively; position 34 was exclusively in VP1; the remaining surface positions were located in putative loop regions of VP3. The remaining mutants, most of them partially defective, were presumably defective in steps of viral entry that were not tested in the preliminary screening, including intracellular trafficking, viral uncoating, or coreceptor binding. Finally, in vitro experiments showed that insertion of the **serpin** receptor ligand in the N-terminal regions of VP1 or VP2 can change the tropism of AAV. Our results provide information on AAV capsid functional domains and are useful for future design of AAV vectors for targeting of specific tissues.

L14 ANSWER 6 OF 49 MEDLINE
ACCESSION NUMBER: 2000110566 MEDLINE
DOCUMENT NUMBER: 20110566 PubMed ID: 10646646
TITLE: Improved production of adenovirus vectors expressing apoptotic transgenes.
AUTHOR: Bruder J T; Appiah A; Kirkman W M 3rd; Chen P; Tian J; Reddy D; Brough D E; Lizonova A; Kovesdi I
CORPORATE SOURCE: GenVec, Inc., Gaithersburg, MD 20878, USA.. bruder@genvec.com
SOURCE: HUMAN GENE THERAPY, (2000 Jan 1) 11 (1) 139-49.
Journal code: 9008950. ISSN: 1043-0342.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000229

Last Updated on STN: 20000229
Entered Medline: 20000211

AB Adenovirus vectors expressing gene products that can induce apoptosis have potential utility in **gene therapy** applications ranging from the treatment of proliferative diseases to transplantation. However, adenovirus vectors carrying proapoptotic gene products are difficult to produce, as the apoptotic environment is not conducive to adenovirus gene expression and replication. Production of AdFasL/G, an adenovirus vector that expresses high levels of Fas ligand, was severely reduced in the 293 packaging cell line. Increased yields of AdFasL/G were achieved by inclusion of peptide-based caspase inhibitors in the growth medium. However, use of these inhibitors for large-scale production would be difficult and expensive. A screen for gene products that increase the yield of AdFasL/G in 293 cells revealed that the poxvirus **serpin** CrmA and the adenovirus 14.7K product were able to increase virus yields significantly. Apoptosis induced by AdFasL/G was attenuated in 293CrmA cell lines and virus titers were increased dramatically. However, serial passage of AdFasL/G on 293CrmA cells resulted in the generation of replication-competent adenovirus. To resolve this problem, the CrmA gene was introduced into AE25 cells, an E1-complementing cell line that has limited sequence identity with the vectors. AdFasL/G titers were increased 100-fold on AE25CrmA cells relative to the AE25 cells and RCA contamination was not detectable. In addition, adenovirus vectors that express FADD, caspase 8, and Fas/APO1 were produced efficiently in AE25CrmA and 293CrmA.

L14 ANSWER 7 OF 49 MEDLINE
ACCESSION NUMBER: 1999139037 MEDLINE
DOCUMENT NUMBER: 99139037 PubMed ID: 9971837
TITLE: Development of animal models for adeno-associated virus site-specific integration.
AUTHOR: Rizzuto G; Gorgoni B; Cappelletti M; Lazzaro D; Gloaguen I; Poli V; Sgura A; Cimini D; Ciliberto G; Cortese R; Fattori E; La Monica N
SOURCE: JOURNAL OF VIROLOGY, (1999 Mar) 73 (3) 2517-26.
Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990316
Last Updated on STN: 19990316
Entered Medline: 19990304

AB The adeno-associated virus (AAV) is unique in its ability to target viral DNA integration to a defined region of human chromosome 19 (AAVS1). Since AAVS1 sequences are not conserved in a rodent's genome, no animal model is currently available to study AAV-mediated site-specific integration. We describe here the generation of transgenic rats and mice that carry the AAVS1 3.5-kb DNA fragment. To test the response of the transgenic animals to Rep-mediated targeting, primary cultures of mouse fibroblasts, rat hepatocytes, and fibroblasts were infected with wild-type wt AAV. PCR amplification of the inverted terminal repeat (ITR)-AAVS1 junction revealed that the AAV genome integrated into the AAVS1 site in fibroblasts and hepatocytes. Integration in rat fibroblasts was also observed upon transfection of a plasmid containing the rep gene under the control of the p5 and **p19** promoters and a dicistronic cassette carrying the green fluorescent protein (GFP) and neomycin (neo) resistance gene between the ITRs of AAV. The localization of the GFP-Neo sequence in the AAVS1 region was determined by Southern blot and FISH analysis. Lastly, AAV genomic DNA integration into the AAVS1 site in vivo was assessed by virus injection into the quadriceps muscle of transgenic rats and mice. Rep-mediated targeting to the AAVS1 site was detected in several injected animals. These results indicate that the transgenic lines are proficient for Rep-mediated targeting. These animals should allow further characterization of the molecular aspects of site-specific integration and testing of the efficacy of targeted integration of AAV recombinant vectors designed for human **gene therapy**.

L14 ANSWER 8 OF 49 MEDLINE

ACCESSION NUMBER: 97423494 MEDLINE
DOCUMENT NUMBER: 97423494 PubMed ID: 9277436
TITLE: Gene transfer into hepatoma cell lines via the serpin enzyme complex receptor.
AUTHOR: Ziady A G; Perales J C; Ferkol T; Gerken T; Beegen H; Perlmutter D H; Davis P B
CORPORATE SOURCE: Department of Physiology and Biophysics, Case Western Reserve University School of Medicine, Cleveland, Ohio 44106, USA.
CONTRACT NUMBER: DK-43999 (NIDDK)
DK-49138 (NIDDK)
P30-DK-27651 (NIDDK)
+
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, (1997 Aug) 273 (2 Pt 1) G545-52.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19971008
Last Updated on STN: 19971008
Entered Medline: 19970924

AB The **serpin** enzyme complex receptor (SECR) expressed on hepatocytes binds to a conserved sequence in alpha 1-antitrypain (alpha 1-AT) and other **serpins**. A molecular conjugate consisting of a synthetic peptide (C1315) based on the SECR binding motif of human alpha 1-AT covalently coupled to poly-L-lysine was used to introduce reporter genes into hepatoma cell lines in culture. This conjugate condensed DNA into spheroidal particles 18-25 nm in diameter. When transfected with the SECR-directed complex containing pGL3, Hep G2 cells that express the receptor, but not Hep G2 cells that do not, expressed a peak luciferase activity of 538,731 +/- 144,346 integrated light units/mg protein 4 days after transfection. Free peptide inhibited uptake and expression in a dose-dependent manner. Complexes of DNA condensed with polylysine or LC-sulfo-N-succinimidyl-3-(2-pyridyldithio)propionate-substituted polylysine were ineffective. Transfection with a plasmid encoding human factor IX produced expression in Hep G2 (high) and HuH7 cells that express SECR but not Hep G2 (low) cells that lack the receptor. Fluorescein-labeled C1315 peptide labeled 9-31% of Hep G2 (high), 10-14% of HuH7, and 0.6-3.4% of Hep G2 (low) cells, and when the lac Z gene was transfected, only these cells expressed beta-galactosidase. SECR-mediated gene transfer gives efficient, specific uptake and high-level expression of three reporter genes, and the system merits further study for **gene therapy**.

L14 ANSWER 9 OF 49 MEDLINE
ACCESSION NUMBER: 97200266 MEDLINE
DOCUMENT NUMBER: 97200266 PubMed ID: 9048201
TITLE: Adenovirus-mediated delivery of human kallistatin gene reduces blood pressure of spontaneously hypertensive rats.
AUTHOR: Chen L M; Chao L; Chao J
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, Medical University of South Carolina, Charleston 29425-2211, USA.
CONTRACT NUMBER: HL 44083 (NHLBI)
SOURCE: HUMAN GENE THERAPY, (1997 Feb 10) 8 (3) 341-7.
Journal code: 9008950. ISSN: 1043-0342.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 19970902
Last Updated on STN: 20000303
Entered Medline: 19970821

AB Human kallistatin, or human tissue kallikrein-binding protein (HKBP), is a serine proteinase inhibitor (**serpin**). Transgenic mice overexpressing rat kallikrein-binding protein are hypotensive. To elucidate therapeutic potentials of kallistatin in hypertension, the human

kallistatin gene in an adenoviral vector was directly introduced into spontaneously hypertensive rats (SHR) through portal vein injection. The kallistatin cDNA construct (RSV-cHKBP) under the promoter control of Rous sarcoma virus 3' long terminal repeat (LTR) was incorporated into adenovirus (Ad.RSV-cHKBP). Recombinant kallistatin in 293 cells transfected with RSV-cHKBP or Ad.RSV-cHKBP was measured by ELISA and by its complex formation with tissue kallikrein. A single intraportal vein injection of Ad.RSV-cHKBP at a dose of 8 x 10(10) pfu results in a significant reduction of blood pressure of SHR for 4 weeks. Human kallistatin mRNA was detected in the liver, spleen, kidney, aorta, and lung of rats receiving gene delivery. Immunoreactive human kallistatin in rat serum was detected at the highest level 1 day post injection and at lesser amounts in rat tissues. This study shows that adenovirus harboring Ad.RSV-cHKBP produces functional kallistatin, and adenovirus-mediated transfer of the human kallistatin gene reduces blood pressures of SHR. The results suggest that kallistatin may function as a vasodilator in vivo and provide important information for a potential **gene therapy** approach to hypertension.

L14 ANSWER 10 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:927561 CAPLUS
DOCUMENT NUMBER: 138:20479
TITLE: Generating replication defective circular adeno-associated viral vectors that are helper free for gene therapy
INVENTOR(S): Kaplitt, Michael G.; Moussatov, Sergei
PATENT ASSIGNEE(S): The Rockefeller University, USA
SOURCE: PCT Int. Appl., 69 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002097056	A2	20021205	WO 2002-US17324	20020531

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-294797P P 20010531
US 2001-313007P P 20010807

AB The present invention provides a method of producing defective viral vectors for gene therapy that are completely free of helper viral vectors and helper viruses. The invention further provides new circular AAV vectors which are particularly useful for use in gene therapy and prodn. stocks of packaged defective viral vectors. Sequences are provided that are capable of directing circular adeno-assocd. virus replication, useful in vectors for providing therapeutic agents to a subject for gene therapy. The vectors of the invention are particularly useful in treatment of acute medical conditions requiring rapid gene expression. Further provided are methods for producing packaged defective viral vectors.

L14 ANSWER 11 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:574872 CAPLUS
DOCUMENT NUMBER: 137:145531
TITLE: Serpin drugs for treatment of HIV infection and method of use thereof
INVENTOR(S): Lynn, Ralf Geiben; Walker, Bruce D.
PATENT ASSIGNEE(S): The General Hospital Corporation, USA
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002058638	A2	20020801	WO 2002-US2309	20020125
WO 2002058638	A3	20020926		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2002127698	A1	20020912	US 2002-57613	20020125

PRIORITY APPLN. INFO.: US 2001-264338P P 20010126

AB The invention includes compns. comprising substantially purified serpin that are useful in methods for the treatment and prevention of HIV infection. The invention also includes methods for the treatment and prevention of HIV infection comprising contacting a compn. of the invention with a human patient or treating HIV infection by introducing into a cell susceptible to HIV infection a DNA mol. encoding a serpin. Addnl., the invention includes antibodies and kits useful in the detection, treatment, and prevention of HIV infection.

L14 ANSWER 12 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:461284 CAPLUS
DOCUMENT NUMBER: 137:42639
TITLE: ARF-p19 protein, a novel regulator of the mammalian cell cycle and its use as a tumor suppressor
INVENTOR(S): Sherr, Charles J.; Quelle, Dawn; Roussel, Martine F.; Zindy, Frederique; Weber, Jason D.
PATENT ASSIGNEE(S): St. Jude Children's Research Hospital, USA
SOURCE: U.S., 105 pp., Cont.-in-part of U.S. Ser. No. 129,855.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6407062	B1	20020618	US 2000-480718	20000107
US 5723313	A	19980303	US 1995-534975	19950927
US 5876965	A	19990302	US 1997-954470	19971020
US 6046032	A	20000404	US 1998-129855	19980806
US 6482929	B1	20021119	US 2000-610833	20000706

PRIORITY APPLN. INFO.: US 1995-534975 A3 19950927
US 1997-954470 A2 19971020
US 1998-129855 A2 19980806
US 1999-247154 A3 19990209

AB The INK4A (MTS1, CDKN2) gene encodes a specific inhibitor (InK4a-p16) of the cyclin D-dependent kinases CDK4 and CDK6. InK4a-p16 can block these kinase from phosphorylating the retinoblastoma protein (pRb), preventing exit from the G1 phase of the cell cycle. Deletions and mutations involving the gene encoding InK4a-p16, INK4A, occur frequently in cancer cells, implying that INK4a-p16, like pRb, suppresses tumor formulation. However, a completely unrelated protein (ARF-p19) arises in major part from an alternative reading frame of the mouse INK4A gene. Expression of an ARF-p19 cDNA in rodent fibroblasts induces both G1 and G2 phase arrest. Economical reutilization of protein coding sequences in this manner is without precedent in mammalian genomes, and the unitary inheritance of INK4a-p16 and ARF-p19 may reflect a dual requirement for both proteins in cell cycle control.

REFERENCE COUNT: 124 THERE ARE 124 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 13 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:391862 CAPLUS
DOCUMENT NUMBER: 136:382192
TITLE: Polynucleotide encoding a novel human serpin LSI-01 secreted from lymphoid cells
INVENTOR(S): Chen, Jian; Feder, John N.; Nelson, Thomas; Seiler, Steven; Bassolino, Donna A.; Cheney, Daniel L.; Duclos, Frank
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: PCT Int. Appl., 478 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002040654	A2	20020523	WO 2001-US43965	20011114
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002017838	A5	20020527	AU 2002-17838	20011114

PRIORITY APPLN. INFO.:		
US 2000-248434P	P	20001114
US 2000-257610P	P	20001221
US 2001-282745P	P	20010410
WO 2001-US43965	W	20011114

AB The present invention provides novel polynucleotides encoding LSI-01 (Lymphocyte Specific proteinase Inhibitor-01) polypeptides, fragments and homologs thereof. To search for novel protease inhibitors, a Hidden-Markov Model of serine protease inhibitors was used to search against human genomic sequence database using the computer program GENEWISEDB; genomic sequences that received a matching score of more than 15 against SERPIN HMM model were selected for further anal. The human sequence encodes a serine proteinase inhibitor (serpin) with substantial homol. to the class of serpins having a protease specificity for arginine/lysine residues. In addn., expression anal. indicates that LSI-091 has strong preferential expression in lymph nodes, and to a lesser extent, in thymus, small intestine, and spleen. The Serpin LSI-01 cDNA was mapped to chromosome region 14q32. Based on its expression profile and genetic map, Serpin LSI-01 could be a novel specific biomarker that could pinpoint a subgroup of patients with chronic lymphocytic leukemias (with a distinct prognostic). Also provided are vectors, host cells, antibodies, and recombinant and synthetic methods for producing said polypeptides. The invention further relates to diagnostic and therapeutic methods for applying these novel LSI-01 polypeptides to the diagnosis, treatment, and/or prevention of various diseases and/or disorders related to these polypeptides. The invention further relates to screening methods for identifying agonists and antagonists of the polynucleotides and polypeptides of the present invention.

L14 ANSWER 14 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:275061 CAPLUS
DOCUMENT NUMBER: 137:179820
TITLE: Functional evidence of CFTR gene transfer in nasal epithelium of cystic fibrosis mice in vivo following luminal application of DNA complexes targeted to the serpin-enzyme complex receptor
AUTHOR(S): Ziady, Assem-Galal; Kelley, Thomas J.; Milliken, Erin; Ferkol, Thomas; Davis, Pamela B.
CORPORATE SOURCE: Departments of Pediatrics at Rainbow Babies and Childrens Hospital, Case Western Reserve University School of Medicine, Cleveland, OH, 44106, USA

SOURCE: Molecular Therapy (2002), 5(4), 413-419
CODEN: MTOHCK; ISSN: 1525-0016
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mol. conjugates that target the serpin-enzyme complex receptor transfer the cDNA encoding human cystic fibrosis transmembrane conductance regulator (CFTR) to the nasal epithelium of cystic fibrosis mutant mice. These complexes effect partial correction of the chloride transport defect as assessed by in vivo nasal p.d. measurements, produce immunohistochem. staining for CFTR, and restore expression of nitric oxide synthase-2 (NOS-2), which is downregulated in the epithelium of mice and humans with cystic fibrosis. Complexes that lack the receptor ligands were ineffective, so receptor access was essential. Mice treated with receptor-targeted lacZ showed .beta.-galactosidase expression, in epithelial cells and submucosal glands, but no electrophysiol. correction or NOS-2 expression, so simply accessing the serpin-enzyme complex receptor was not sufficient to produce the obsd. electrophysiol. or immunohistochem. changes. Correction of the cAMP-stimulated chloride transport was dose related at days 7 and 12 after complex administration, but, for most animals, nasal p.d. had returned to baseline by day 18. Mol. conjugates targeting the serpin-enzyme complex receptor, used to compact plasmid DNA, hold promise for **gene therapy** of cystic fibrosis.
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 15 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:870909 CAPLUS
DOCUMENT NUMBER: 137:88832
TITLE: Receptor-directed molecular conjugates for gene transfer
AUTHOR(S): Ziady, Assem G.; Davis, Pamela B.
CORPORATE SOURCE: Department of Pediatrics at Rainbow Babies and Children's Hospital, School of Medicine, Case Western Reserve University, Cleveland, OH, USA
SOURCE: Methods in Molecular Medicine (2002), 69(Gene Therapy Protocols (2nd Edition)), 25-48
CODEN: MMMEFN
PUBLISHER: Humana Press Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB This review provides methods for using receptor-mediated mol. conjugate for gene transfer are described. DNA, noncovalently bound to a polycation polymer that is conjugated to a ligand can be bound to the cell surface and internalized. Receptor-directed mol. conjugates have use as gene therapy agents. The use of such receptors, which have provided specificity of a noninfectious and nontoxic vector, are discussed. The method include generation of receptor-targeted mol. conjugates, mol. conjugate anal., receptor-targeted DNA complex prodn., and anal. of receptor-targeted DNA complexes.
REFERENCE COUNT: 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 16 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:598149 CAPLUS
DOCUMENT NUMBER: 135:177276
TITLE: Protein C derivatives with increased anti-coagulation activity and resistance to inactivation by serpins and their pharmacological use
INVENTOR(S): Gerlitz, Bruce Edward; Grinnell, Brian William; Jones, Bryan Edward
PATENT ASSIGNEE(S): Eli Lilly and Company, USA
SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001059084	A1	20010816	WO 2001-US1221	20010202
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1263943	A1	20021211	EP 2001-904860	20010202
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2003022354	A1	20030130	US 2002-182263	20020722

PRIORITY APPLN. INFO.: US 2000-181948P P 20000211
US 2000-189199P P 20000314
WO 2001-US1221 W 20010202

AB Novel human protein C derivs. are described. These derivs. have increased anti-coagulation activity, resistance to serpin inactivation, and increased sensitivity to thrombin activation compared to wild-type protein C and retain the biol. activity of the wild-type human protein C. These derivs. will require either less frequent administration and/or smaller dosage than wild-type human protein C in the treatment of acute coronary syndromes, vascular occlusive disorders, hypercoagulable states, thrombotic disorders and disease states predisposing to thrombosis.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 17 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:582029 CAPLUS
DOCUMENT NUMBER: 135:164093
TITLE: Protein C derivatives with increased anti-coagulation activity and resistance to inactivation by serpins and their pharmacological use
INVENTOR(S): Gerlitz, Bruce Edward; Jones, Bryan Edward
PATENT ASSIGNEE(S): Eli Lilly and Company, USA
SOURCE: PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001057193	A2	20010809	WO 2001-US20	20010119
WO 2001057193	A3	20020207		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1255821	A2	20021113	EP 2001-904786	20010119
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: US 2000-179801P P 20000202
US 2000-189197P P 20000314
WO 2001-US20 W 20010119

AB Novel human protein C derivs. are described. These derivs. have increased anti-coagulation activity and resistance to inactivation by serpins compared to wild-type protein C and retain the biol. activity of the wild-type human protein C. These derivs. will require either less frequent administration and/or smaller dosage than wild-type human protein C in the treatment of acute coronary syndromes, vascular occlusive

disorders, hypercoagulable states, thrombotic disorders and disease states predisposing to thrombosis.

L14 ANSWER 18 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:101002 CAPLUS
DOCUMENT NUMBER: 134:168342
TITLE: Enhanced delivery via serpin enzyme complex receptor
INVENTOR(S): Ziady, Assem; Davis, Pamela B.; Ferkol, Thomas W., Jr.; Malouf, Alfred
PATENT ASSIGNEE(S): Case Western Reserve University, USA
SOURCE: PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001008708	A2	20010208	WO 2000-US20545	20000728
WO 2001008708	A3	20020124		
W: AU, CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1200616	A2	20020502	EP 2000-948981	20000728
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
JP 2003505518	T2	20030212	JP 2001-513438	20000728

PRIORITY APPLN. INFO.: US 1999-145970P P 19990729
WO 2000-US20545 W 20000728

AB Serpin enzyme complex receptors (SEC-R) are used as targets for therapeutic drugs in the lungs and brain tissue. Any lung or brain disease and any therapeutic drug can be targeted to the lung or brain by use of ligands which specifically bind to the receptors. Complexes for delivery may include proteins, pharmacol. agents, or nucleic acids, as well as carrier mols., and ligands for the receptors. The ligands can be coupled directly to the therapeutic agent or to a carrier mol. which binds to the therapeutic agent. For example, the ability to transfer genes into airway epithelial cell via SEC-R was studied using in vitro models. Two human airway epithelial cell line, 9HTEo-(which does not form tight junctions) and 16HBEEo-cells (which do form tight junctions) can be transfected with SEC-R directed complexes, though these expts. were done with cells grown on plastic and not polarized. These cells never achieve the high levels of expression seen in human hepatoma HuH7 cells, nor is the duration of expression as long. To further pursue the observations, human tracheal epithelial cells were grown in primary cultures to confluence on filters, and demonstrated that they formed a polarized monolayer. Using fluorescein-tagged C105Y peptide, it was demonstrated that there was binding of the peptide to the apical surface of airway epithelial cells. Moreover, the transfer of a reporter gene, green fluorescent protein, to primary cultures of polarized human airway epithelial cells was possible by using SEC-R directed complexes applied to the apical surface. Interestingly, in vitro, C1315 ligand was as efficacious as C105Y. It was these data that encouraged the authors to test the ability to correct the CF mouse in vivo. These data also indicate that this system accesses human airway epithelial cells as well as mouse airway epithelial cells.

L14 ANSWER 19 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:841957 CAPLUS
DOCUMENT NUMBER: 133:366470
TITLE: Methods and compositions for non-viral gene therapy for treatment of hyperproliferative diseases
INVENTOR(S): Ramesh, Rajagopal; Roth, Jack A.; Saeki, Tomoyuki; Wilson, Deborah
PATENT ASSIGNEE(S): Introgen Therapeutics, Inc., USA; Board of Regents, the University of Texas System
SOURCE: PCT Int. Appl., 148 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000071096	A2	20001130	WO 2000-US14350	20000524
WO 2000071096	A3	20010503		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1180016	A2	20020220	EP 2000-936279	20000524

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, MC, PT, IE, SI, LT, LV, FI, RO

PRIORITY APPLN. INFO.: US 1999-135818P P 19990524
WO 2000-US14350 W 20000524

AB The present invention relates to non-viral gene therapy methods and compns. for treatment of hyperproliferative disease in humans. More specifically, the invention is directed, in one embodiment, to lipid formulations which form stable liposome structures, capable of efficient in vivo nucleic acid transfer. In other embodiments, methods and compns. are directed to liposome transfer of anti-proliferative nucleic acids, wherein the transfer of the nucleic acids is cell specific via cell specific targeting moieties. The present invention thus provides non-viral, liposome compns. and methods of gene transfer particularly useful for targeting and treating hyperproliferative disease.

L14 ANSWER 20 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:628265 CAPLUS
DOCUMENT NUMBER: 133:218537
TITLE: Human serpin homolog-encoding polynucleotides and their encoded proteins
INVENTOR(S): Ruben, Steven M.; Ni, Jian
PATENT ASSIGNEE(S): Human Genome Sciences, Inc., USA
SOURCE: PCT Int. Appl., 215 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000052160	A1	20000908	WO 2000-US5082	20000229

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1161532	A1	20011212	EP 2000-914744	20000229

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

JP 2002537810	T2	20021112	JP 2000-602772	20000229
WO 2001055390	A1	20010802	WO 2001-US2484	20010126

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2002160491	A1	20021031	US 2001-912628		20010726
US 2003040097	A1	20030227	US 2002-116166		20020405

PRIORITY APPLN. INFO.:

US 1999-122276P	P	19990301
US 1999-124094P	P	19990312
US 1999-149452P	P	19990818
US 2000-178769P	P	20000128
WO 2000-US5082	W	20000229
US 2000-641721	A1	20000821
WO 2001-US2484	A2	20010126

AB The present invention relates to two novel human serpin homolog polypeptides and isolated nucleic acids contg. the coding regions of the genes encoding such polypeptides. The translation product of one such cDNA shares sequence homol. with rat RASP1 (regeneration assocd. serpin-1) and the gene is located on chromosome 14. This cDNA was isolated from a human liver cDNA library, and is expressed in primary dendritic cells, activated T-cells, bone marrow tissue, endometrial tumor tissue, rejected kidney tissue, pancreas tumor tissue, neutrophils, PMBC stimulated with poly(I)-poly(C), and ovaries, and to a lesser extent in a variety of normal and transformed cell types. The 2nd cDNA encodes a translation product with sequence homol. with a human thrombin inhibitor thought to be important in apoptosis, and is expressed primarily in healing abdomen wound tissue, human adrenal gland tumor tissue, and macrophage-oxLDL, and to a lesser extent in KMH2 and TNF-induced amniotic cells. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human Serpin polypeptides. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to these novel human serpin polypeptides.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 21 OF 49 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:535300 CAPLUS

DOCUMENT NUMBER: 133:145943

TITLE: E1b-deleted adenoviral shuttle vectors for cancer gene therapy

INVENTOR(S): Hermiston, Terry; Nye, Julie

PATENT ASSIGNEE(S): Onyx Pharmaceuticals, Inc., USA

SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000044922	A1	20000803	WO 2000-US2029	20000126

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2360355	AA	20000803	CA 2000-2360355	20000126
EP 1135514	A1	20010926	EP 2000-907050	20000126

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

PRIORITY APPLN. INFO.:

US 1999-117814P	P	19990128
WO 2000-US2029	W	20000126

AB Provided are replication competent, recombinant adenovirus vectors contg. mutations in the E1B region which permit the easy deletion of a gene or genes therein, and optionally the substitution therefore of a heterologous gene that substantially exhibits the temporal expression pattern of the E1b region gene(s) deleted. The E1b deletion region are selected from p19, 55K and pIX which can be substituted with a gene that encodes

cytosine deaminase, thymidine kinase, or heterologous proteins selected from the group consisting of TNF.alpha., interferon .gamma., an interleukin, a cell suicide protein, and MIP-3. Such vectors have applications for the treatment of disease, and preferably for the treatment of neoplastic disease.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 22 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:723172 CAPLUS
DOCUMENT NUMBER: 131:334127
TITLE: human cytoplasmic antiproteinase-3 coding sequence and applications for gene therapy
INVENTOR(S): Sprecher, Cindy A.; Foster, Donald C.; Jaspers, Stephen R.
PATENT ASSIGNEE(S): Zymogenetics, USA
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9957273	A2	19991111	WO 1999-US8949	19990427
WO 9957273	A3	20000120		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6392190	B1	20020521	US 1998-153676	19980915
GB 2333482	A1	19990728	GB 1999-80	19990104
GB 2333482	B2	20020619		
AU 9938667	A1	19991123	AU 1999-38667	19990427

PRIORITY APPLN. INFO.:
US 1998-72275P P 19980504
US 1998-72275 A 19980504
US 1998-153676 A 19980915
WO 1999-US8949 W 19990427

AB Cytoplasmic antiproteinase-3 nucleic acids and serine and cysteine protease inhibitor proteins encoded thereby useful in the purifn. of proteins and in the treatment of inflammatory diseases and diseases involving apoptosis are provided. A method for modulating apoptosis mediated by caspase-4 in an individual is achieved by administering a ligand which binds to expression product of gene for intracellular mammalian serpin sufficient to alter activity of caspase-4. The method includes providing a non-integrating DNA construct which comprises an operably linked transcriptional promoter, a DNA segment encoding a polypeptide which inhibits serine or cysteine proteinase activity and a transcriptional terminator to an individual with a caspase-mediated disease. Diseases may include neurodegenerative diseases or lung disease etc. Methods for treating such diseases mediated by a caspase by administering a host gene encoding a mammalian serpin are described. This work relates to treating a disease or symptoms of a disease mediated by a caspase by transiently expressing a proteinaceous anticaspase gene in a diseased target tissue. This work is exemplified by the use of cytoplasmic antiproteinase-3 (CAP-3) to inhibit interleukin-1.beta.-converting enzyme and plasminogen activator inhibitor-2. High gene expression of CAP-3 was found in lung and placenta.

L14 ANSWER 23 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:686690 CAPLUS
DOCUMENT NUMBER: 131:327493
TITLE: Serpin enzyme complex receptor-mediated gene transfer
INVENTOR(S): Ferkol, Thomas W., Jr.; Davis, Pamela B.; Ziady, Assem-galal

PATENT ASSIGNEE(S): Case Western Reserve University, USA
SOURCE: U.S., 81 pp., Cont.-in-part of U.S. Ser. No. 655,705.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5972901	A	19991026	US 1996-656906	19960603
WO 9525809	A1	19950928	WO 1995-US3677	19950323
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TT				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5972900	A	19991026	US 1996-655705	19960603
WO 9746100	A1	19971211	WO 1997-US9858	19970603
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9733044	A1	19980105	AU 1997-33044	19970603
AU 720223	B2	20000525		
EP 1006797	A1	20000614	EP 1997-928891	19970603
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2000512140	T2	20000919	JP 1998-500875	19970603
US 6072041	A	20000606	US 1997-957333	19971024
US 6261787	B1	20010717	US 1999-264032	19990308
US 6287817	B1	20010911	US 2000-559393	20000426

PRIORITY APPLN. INFO.:
US 1994-216534 B2 19940323
WO 1995-US3677 A1 19950323
US 1996-655705 A2 19960603
US 1996-656906 A 19960603
WO 1997-US9858 W 19970603
US 1997-957333 A2 19971024

AB Nucleic acids are compacted, substantially without aggregation, to facilitate their uptake by target cells of an organism to which the compacted material is administered. The nucleic acids may achieve a clin. effect as a result of gene expression, hybridization to endogenous nucleic acids whose expression is undesired, or site-specific integration so that a target gene is replaced, modified or deleted. The targeting may be enhanced by means of a target cell-binding moiety. The nucleic acid is preferably compacted to a condensed state.

REFERENCE COUNT: 79 THERE ARE 79 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 24 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:511240 CAPLUS
DOCUMENT NUMBER: 131:140506
TITLE: Cloning and sequences of cDNAs encoding human serine protease and serpin polypeptides
INVENTOR(S): Ruben, Steven M.; Ni, Jian
PATENT ASSIGNEE(S): Human Genome Sciences, Inc., USA
SOURCE: PCT Int. Appl., 99 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9940183	A1	19990812	WO 1999-US2292	19990204
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR,				

TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2319644	AA	19990812	CA 1999-2319644	19990204
AU 9925776	A1	19990823	AU 1999-25776	19990204
EP 1054958	A1	20001129	EP 1999-905666	19990204
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002502600	T2	20020129	JP 2000-530597	19990204
PRIORITY APPLN. INFO.:			US 1998-73961P	P 19980206
			WO 1999-US2292	W 19990204

AB The present invention relates to novel human secreted proteins and isolated nucleic acids contg. the coding regions of the genes encoding such proteins. Three of the encoded polypeptides are members of the serine protease polypeptide family, based on a strong degree of sequence similarity, whereas another 3 polypeptides are members of the serpin polypeptide family. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to these novel human secreted proteins.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 25 OF 49 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:797668 CAPLUS
DOCUMENT NUMBER: 130:148359
TITLE: Ligand substitution of receptor targeted DNA complexes affects gene transfer into hepatoma cells
AUTHOR(S): Ziady, A-G.; Ferkol, T.; Gerken, T.; Dawson, D. V.; Perlmutter, D. H.; Davis, P. B.
CORPORATE SOURCE: Department of Physiology and Biophysics, Case Western Reserve University School of Medicine, Cleveland, OH, 44106-6006, USA
SOURCE: Gene Therapy (1998), 5(12), 1685-1697
CODEN: GETHEC; ISSN: 0969-7128
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors have targeted the serpin enzyme complex receptor for gene transfer in human hepatoma cell lines using peptides <30 amino acids in length which contain the five amino acid recognition sequence for this receptor, coupled to poly K of av. chain length 100 K, using the heterobifunctional coupling reagent sulfo-LC SPDP. The no. of sulfo-LC SPDP modified poly-L-lysine residues, as well as the degree of peptide substitution was assessed by NMR spectroscopy. Conjugates were prepd. in which 3.5%, 7.8% or 26% of the lysine residues contained the sulfo-LC SPDP moiety. Each of these conjugates was then coupled with ligand peptides so that one in 370, one in 1039, or one in 5882 lysines were substituted with receptor ligand. Electron microscopy and at. force microscopy were used to assess complex structure and size. HuH7 human hepatoma cells were transfected with complexes of these conjugates with the plasmid pGL3 and luciferase expression measured 2 to 16 days after treatment. All the protein conjugates in which 26% of the K residues were modified with sulfo-LC SPDP were poor gene transfer reagents. Complexes contg. less substituted poly K, averaged 17 .+-. 0.5 nm in diam. and gave peak transgene expression of 3-4 .times. 106 ILU/mg which persisted (> 7 .times. 105 ILU) at 16 days. Of these, more substituted polymers condensed DNA into complexes averaging 20 .+-. 0.7 nm in diam. and gave five-fold less luciferase than complexes contg. less substituted conjugates. As few as eight to 11 ligands per complex are optimal for DNA delivery via the SEC receptor. The extent of substitution of receptor-mediated gene transfer complexes affects the size of the complexes, as well as the intensity and duration of transgene expression. These observations may permit tailoring of complex construction for the usage required.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 26 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:682550 CAPLUS
DOCUMENT NUMBER: 129:286758
TITLE: Recombinant vectors with improved packaging capacity derived from adeno-associated virus and their use in gene therapy
INVENTOR(S): Ciliberto, Gennaro; Colloca, Stefano; Fattori, Elena; Fipaldini, Cristina; La, Monica Nicola; Monciotti, Andrea; Palombo, Fabio; Pieroni, Luisa; Recchia, Alessandra; Rizzuto, Gabriella
PATENT ASSIGNEE(S): Istituto Di Ricerche Di Biologia Molecolare P. Angeletti S.P.A., Italy; La Monica, Nicola; et al.
SOURCE: PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9845462	A1	19981015	WO 1998-IT82	19980408
W: AU, CA, CN, IL, JP, KR, MX, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9870778	A1	19981030	AU 1998-70778	19980408
CA 2326847	AA	19991021	CA 1999-2326847	19990408
WO 9953084	A1	19991021	WO 1999-EP2384	19990408
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9939265	A1	19991101	AU 1999-39265	19990408
AU 752811	B2	20021003		
EP 1068343	A1	20010117	EP 1999-922090	19990408
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6521426	B1	20030218	US 2000-647795	20001208

PRIORITY APPLN. INFO.:
IT 1997-RM200 A 19970408
WO 1998-IT82 W 19980408
GB 1998-13670 A 19980624
WO 1999-EP2384 W 19990408

AB The present invention refers to vectors derived form recombinant Adeno-assocd. virus (AVV) which comprise at least one selected transgene between the sequences of the 5' and 3' inverted terminal repeats (ITRs) from AAV, and a DNA sequence encoding one or more AAV Rep protein, or a fragment or a deriv. thereof, outside of the context of the AAV ITRs. These vectors have a larger packaging capacity and prior art vectors. The vectors according to the invention are useful in gene therapy. Thus, plasmid pITR(GFP-Neo)P5Rep was prepd. and HeLa cells were transfected with it. This plasmid contains the GFP gene under control of the CMV early promoter and the neomycin resistance gene under control of the SV40 early promoter between the 3'- and 5'-ITRs and the Rep gene controlled by the P5 and P19 promoters outside of the ITRs. The ITR-flanked expression construct was inserted into the HeLa cell genome in a Rep-dependent manner at the aavs1 site.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 27 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:543148 CAPLUS
DOCUMENT NUMBER: 129:174686
TITLE: Human regeneration-associated serpin-1 (RASP-1) and antibodies for treatment of cell proliferation disorders

INVENTOR(S): Purchio, Anthony F.
PATENT ASSIGNEE(S): Hepatix Inc., USA
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9833890	A1	19980806	WO 1998-US1962	19980203
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9862620	A1	19980825	AU 1998-62620	19980203
EP 1015559	A1	20000705	EP 1998-904837	19980203
R: AT, BE, CH, DE, DK, FR, GB, IT, LI, NL, SE, FI				
JP 2001511005	T2	20010807	JP 1998-533174	19980203
US 2002142986	A1	20021003	US 2002-62023	20020131

PRIORITY APPLN. INFO.: US 1997-36842P P 19970203
US 1998-38714 A1 19980203
WO 1998-US1962 W 19980203

AB The invention provides human regeneration-assocd. serpin-1 (RASP-1) polypeptide and nucleic acid mols. that encode RASP-1. Also included in the invention are diagnostic and therapeutic methods using RASP-1 polypeptides and nucleic acids.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 28 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:809902 CAPLUS
DOCUMENT NUMBER: 128:79986
TITLE: Serpin enzyme complex receptor-mediated gene transfer
INVENTOR(S): Ferkol, Thomas W., Jr.; Davis, Pamela B.; Ziady, Assem-Galal
PATENT ASSIGNEE(S): Case Western Reserve University, USA
SOURCE: PCT Int. Appl., 157 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9746100	A1	19971211	WO 1997-US9858	19970603
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5972901	A	19991026	US 1996-656906	19960603
AU 9733044	A1	19980105	AU 1997-33044	19970603
AU 720223	B2	20000525		
EP 1006797	A1	20000614	EP 1997-928891	19970603
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2000512140	T2	20000919	JP 1998-500875	19970603

PRIORITY APPLN. INFO.: US 1996-656906 A 19960603
US 1994-216534 B2 19940323
WO 1995-US3677 A1 19950323
US 1996-655705 A2 19960603
WO 1997-US9858 W 19970603

AB Nucleic acids are compacted, substantially without aggregation, to facilitate their uptake by target cells of an organism to which the compacted material is administered. The nucleic acids may achieve a clin. effect as a result of gene expression, hybridization to endogenous nucleic acids whose expression is undesired, or site-specific integration so that a target gene is replaced, modified or deleted. The targeting may be enhanced by means of a target cell-binding moiety. The nucleic acid is preferably compacted to a condensed state.

L14 ANSWER 29 OF 49 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1997:573309 CAPLUS
DOCUMENT NUMBER: 127:257137
TITLE: Gene transfer into hepatoma cell lines via the serpin enzyme complex receptor
AUTHOR(S): Ziady, Assem-Galal; Perales, Jose C.; Ferkol, Thomas; Gerken, Thomas; Beegen, Helga; Perlmutter, David H.; Davis, Pamela B.
CORPORATE SOURCE: Departments of Physiology and Biophysics, Case Western Reserve University School of Medicine, Cleveland, OH, 44106, USA
SOURCE: American Journal of Physiology (1997), 273(2, Pt. 1), G545-G552
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The serpin enzyme complex receptor (SECR) expressed on hepatocytes binds to a conserved sequence in .alpha.1-antitrypsin (.alpha.1-AT) and other serpins. A mol. conjugate consisting of a synthetic peptide (C1315) based on the SECR binding motif of human .alpha.1-AT covalently coupled to poly-L-lysine was used to introduce reporter genes into hepatoma cell lines in culture. This conjugate condensed DNA into spheroidal particles 18-25 nm in diam. When transfected with the SECR-directed complex contg. pGL3, Hep G2 cells that express the receptor, but not Hep G2 cells that do not, expressed a peak luciferase activity of 538,731 .+-. 144,346 integrated light units/mg protein 4 days after transfection. Free peptide inhibited uptake and expression in a dose-dependent manner. Complexes of DNA condensed with polylysine or LC-sulfo-N-succinimidyl-3-(2-pyridyldithio)propionate-substituted polylysine were ineffective. Transfection with a plasmid encoding human factor IX produced expression in Hep G2 (high) and HuH7 cells that express SECR but not Hep G2 (low) cells that lack the receptor. Fluorescein-labeled C1315 peptide labeled 9-31% of Hep G2 (high), 10-14% of HuH7, and 0.6-3.4% of Hep G2 (low) cells, and when the lac Z gene was transfected, only these cells expressed .beta.-galactosidase. SECR-mediated gene transfer gives efficient, specific uptake and high-level expression of three reporter genes, and the system merits further study for gene therapy.

L14 ANSWER 30 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:599082 CAPLUS
DOCUMENT NUMBER: 125:240253
TITLE: Ink4c-p18 and Ink4d-p19, inhibitors of cyclin-dependent kinases CDK4 and CDK6, and uses thereof
INVENTOR(S): Sherr, Charles J.; Downing, James R.; Hirai, Hiroshi; Oduka, Tsukasa
PATENT ASSIGNEE(S): St. Jude Children's Research Hospital, USA
SOURCE: PCT Int. Appl., 91 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9624603	A1	19960815	WO 1996-US1643	19960206
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN				
US 6033847	A	20000307	US 1995-384106	19950206
CA 2212376	AA	19960815	CA 1996-2212376	19960206
AU 9649738	A1	19960827	AU 1996-49738	19960206
EP 808321	A1	19971126	EP 1996-906316	19960206
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
JP 10513359	T2	19981222	JP 1996-524400	19960206

PRIORITY APPLN. INFO.: US 1995-384106 19950206
WO 1996-US1643 19960206

AB Members of the InK4 (Inhibitors of CDK4) family inhibit the activities of specific cyclin D-dependent kinases (CDK4 and/or CDK6), thereby arresting cell cycle progression in G1 phase and preventing chromosomal DNA replication. Disclosed herein are novel mammalian InK4 family members, having apparent mol. masses of 18,000 and 19,000 daltons, designated InK4c-p18 and InK4d-p19, resp., or simply p18 and p19. In particular, the invention provides p19 genes and proteins isolated from murine or human cells and p18 genes and proteins from murine cells. When constitutively expressed in cells, p19 inhibits cyclin D-dependent kinase activity in vivo and induces G1 phase arrest. Materials and methods disclosed herein include (1) nucleic acids that encode p18 or **p19**; (2) methods for detecting nucleic acids encoding p18 or **p19** proteins; (3) methods for producing p18 or **p19** proteins using nucleic acids that encode p18 or **p19**, resp.; (4) purified p18 or **p19** proteins and peptide fragments, oligopeptides, or fusion proteins derived therefrom; (5) methods of inhibiting cells from replicating their chromosomal DNA using purified p18 or **p19** proteins or derivs. thereof; (6) antibodies that specifically bind p18 or **p19**; (7) methods for detecting p18 and **p19** proteins; (8) method of stimulating cell growth by blocking p18 or **p19** expression via antisense oligonucleotides; (9) methods of **gene therapy** using nucleic acids that encode p18 or **p19**; and (10) methods of making transgenic non-human animals that have alterations in the gene encoding p18 or **p19**, or in both genes. The Ink4d gene was mapped to human chromosome 19.

L14 ANSWER 31 OF 49 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002168969 EMBASE
TITLE: RNA interference by expression of short-interfering RNAs and hairpin RNAs in mammalian cells.
AUTHOR: Yu J.-Y.; DeRuiter S.L.; Turner D.L.
CORPORATE SOURCE: D.L. Turner, University of Michigan, C560 MSRB II, 1150 West Medical Center Drive, Ann Arbor, MI 48109-0669, United States. dlturner@umich.edu
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (30 Apr 2002) 99/9 (6047-6052). Refs: 36
ISSN: 0027-8424 CODEN: PNASA6
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Duplexes of 21-nt RNAs, known as short-interfering RNAs (siRNAs), efficiently inhibit gene expression by RNA interference (RNAi) when introduced into mammalian cells. We show that siRNAs can be synthesized by in vitro transcription with T7 RNA polymerase, providing an economical alternative to chemical synthesis of siRNAs. By using this method, we show that short hairpin siRNAs can function like siRNA duplexes to inhibit gene expression in a sequence-specific manner. Further, we find that hairpin siRNAs or siRNAs expressed from an RNA polymerase III vector based on the mouse U6 RNA promoter can effectively inhibit gene expression in mammalian cells. U6-driven hairpin siRNAs dramatically reduced the expression of a neuron-specific .beta.-tubulin protein during the neuronal differentiation of mouse **P19** cells, demonstrating that this approach should be useful for studies of differentiation and neurogenesis. We also observe that mismatches within hairpin siRNAs can increase the strand selectivity of a hairpin siRNA, which may reduce self-targeting of vectors expressing siRNAs. Use of hairpin siRNA expression vectors for RNAi should provide a rapid and versatile method for assessing gene function in mammalian cells, and may have applications in **gene therapy**.

L14 ANSWER 32 OF 49 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002139580 EMBASE
TITLE: Functional evidence of CFTR gene transfer in nasal epithelium of cystic fibrosis mice in vivo following luminal application of DNA complexes targeted to the serpin-enzyme complex receptor.

AUTHOR: Ziady A.-G.; Kelley T.J.; Milliken E.; Ferkol T.; Davis P.B.
CORPORATE SOURCE: P.B. Davis, Department of Pediatrics, Childrens Hospital, Case Western Reserve Univ. Sch. Med., Cleveland, OH 44106, United States. pbd@po.cwru.edu
SOURCE: Molecular Therapy, (2002) 5/4 (413-419).
Refs: 29
ISSN: 1525-0016 CODEN: MTOHCK
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Molecular conjugates that target the **serpin**-enzyme complex receptor transfer the cDNA encoding human cystic fibrosis transmembrane conductance regulator (CFTR) to the nasal epithelium of cystic fibrosis mutant mice. These complexes effect partial correction of the chloride transport defect as assessed by in vivo nasal potential difference measurements, produce immunohistochemical staining for CFTR, and restore expression of nitric oxide synthase-2 (NOS-2), which is downregulated in the epithelium of mice and humans with cystic fibrosis. Complexes that lack the receptor ligands were ineffective, so receptor access was essential. Mice treated with receptor-targeted lacZ showed .beta.-galactosidase expression in epithelial cells and submucosal glands, but no electrophysiologic correction or NOS-2 expression, so simply accessing the **serpin**-enzyme complex receptor was not sufficient to produce the observed electrophysiologic or immunohistochemical changes. Correction of the cAMP-stimulated chloride transport was dose related at days 7 and 12 after complex administration, but, for most animals, nasal potential difference had returned to baseline by day 18. Molecular conjugates targeting the **serpin**-enzyme complex receptor, used to compact plasmid DNA, hold promise for **gene therapy** of cystic fibrosis.

L14 ANSWER 33 OF 49 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001291941 EMBASE
TITLE: Characterization of permanent cell lines that contain the AAV2 rep-cap genes on an Epstein-Barr-virus-based episomal plasmid.
AUTHOR: Neyns B.; Vermeij J.; Teugels E.; De Rijcke M.; Hermonat P.; De Greve J.
CORPORATE SOURCE: J. De Greve, Oncologisch Centrum, Akademisch Ziekenhuis, Vrije Universiteit Brussel, Laarbeeklaan 101, B-1090 Brussels, Belgium. ongdgej@az.vub.ac.be
SOURCE: Intervirology, (2001) 44/4 (255-263).
Refs: 48
ISSN: 0300-5526 CODEN: IVRYAK
COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
016 Cancer
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Recombinant adeno-associated virus (rAAV) has emerged as a promising **gene therapy** vector. Its development, however, has been hampered by the lack of a readily available efficient production method. We investigated the possibility of establishing permanent cell lines for the production of rAAV with a new Epstein-Barr-virus (EBV)-based episomal AAV rep-cap plasmid (pCEP-rep/cap). HeLa and 293 cells were stably transfected with plasmids that carry the AAV2 rep/cap genes under transcriptional control of their endogenous promoters (p5, **p19** and p40) either on the pCEP-rep/cap or an integrated (pIM45) plasmid. For the ease of monitoring transgene expression in live cells, a rAAV vector expressing gfp (the green fluorescent protein gene, rAAV-gfp/neo) was used. Establishment of stable transfected cell lines with these plasmids proved feasible but their usefulness was limited because of their instability. Within 8-12 weeks after their establishment, stably transfected rep-cap cell lines invariably lost their function. In

addition, the rAAV-gfp/neo vector we used was susceptible to mutation in stably transfected HeLa cells. Our observations demonstrate specific problems both at the level of rep/cap gene function and the rAAV genome that can occur with the establishment of rAAV production cell lines. These experiments should aid the further development of efficient rAAV production protocols. Copyright .COPYRGT. 2001 S. Karger AG, Basel.

L14 ANSWER 34 OF 49 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001149119 EMBASE
TITLE: Endogenous angiogenesis inhibitors and their therapeutic implications.
AUTHOR: Cao Y.
CORPORATE SOURCE: Y. Cao, Laboratory of Angiogenesis Research, Microbiology and Tumor Biology Ctr., Karolinska Institute, S-171 77 Stockholm, Sweden. yihai.cao@mtc.ki.se
SOURCE: International Journal of Biochemistry and Cell Biology, (2001) 33/4 (357-369).
Refs: 88
ISSN: 1357-2725 CODEN: IJBBFU
PUBLISHER IDENT.: S 1357-2725(01)00023-1
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
036 Health Policy, Economics and Management
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB A number of endogenous inhibitors targeting the tumor vasculature have recently been identified using in vitro and in vivo antiangiogenesis models. While many of these angiogenesis inhibitors display a broad spectrum of biological actions on several systems in the body, several inhibitors including angiostatin, endostatin, and **serpin** antithrombin seem to act specifically on the proliferating endothelial cell compartment of the newly formed blood vessels. The discovery of these specific endothelial inhibitors not only increases our understanding of the functions of these molecules in the regulation of physiological and pathological angiogenesis, but may also provide an important therapeutic strategy for the treatment of cancer and other angiogenesis dependent diseases, including diabetic retinopathy and chronic inflammations. Systemic administration of these angiogenesis inhibitors in animals significantly suppresses the growth of a variety of tumors and their metastases. However, their production as functional recombinant proteins has been proven to be difficult. In addition, high dosages of these inhibitors are required to suppress tumor growth in animal studies. Other disadvantages of the antiangiogenic protein therapy include repeated injections, prolonged treatment, transmission of toxins and infectious particles, and high cost for manufacturing large amounts of protein molecules. Thus, alternative strategies need to be developed in order to improve the clinical settings of antiangiogenic therapy. Developments of these strategies are ongoing and they include identification of more potent inhibitors, antiangiogenic **gene therapy**, improvement of protein/compound half-lives in the circulation, increase of their concentrations at the disease location, and combinatorial therapies with approaches including chemotherapy, radiotherapy, and immunotherapy. Despite the above-mentioned disadvantages, a few inhibitors have entered into the early stages of clinical trials and they may bring new hopes for the treatment of cancer and other angiogenesis dependent diseases. .COPYRGT. 2001 Elsevier Science Ltd.

L14 ANSWER 35 OF 49 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000309646 EMBASE
TITLE: Mutational analysis of the adeno-associated virus type 2 (AAV2) capsid gene and construction of AAV2 vectors with altered tropism.
AUTHOR: Wu P.; Xiao W.; Conlon T.; Hughes J.; Agbandje-Mckenna M.; Ferkol T.; Flotte T.; Muzyczka N.
CORPORATE SOURCE: N. Muzyczka, Dept. of Molec. Genet. and Microb., College of Medicine, University of Florida, P.O. Box 100266, Gainesville, FL 32610, United States. muzyczka@mgm.ufl.edu

SOURCE: Journal of Virology, (2000) 74/18 (8635-8647).
Refs: 53
ISSN: 0022-538X CODEN: JOVIAM
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Adeno-associated virus type 2 (AAV2) has proven to be a valuable vector for **gene therapy**. Characterization of the functional domains of the AAV capsid proteins can facilitate our understanding of viral tissue tropism, immunoreactivity, viral entry, and DNA packaging, all of which are important issues for generating improved vectors. To obtain a comprehensive genetic map of the AAV capsid gene, we have constructed 93 mutants at 59 different positions in the AAV capsid gene by site-directed mutagenesis. Several types of mutants were studied, including epitope tag or ligand insertion mutants, alanine scanning mutants, and epitope substitution mutants. Analysis of these mutants revealed eight separate phenotypes. Infectious titers of the mutants revealed four classes. Class 1 mutants were viable, class 2 mutants were partially defective, class 3 mutants were temperature sensitive, and class 4 mutants were noninfectious. Further analysis revealed some of the defects in the class 2, 3, and 4 mutants. Among the class 4 mutants, a subset completely abolished capsid formation. These mutants were located predominantly, but not exclusively, in what are likely to be .beta.-barrel structures in the capsid protein VP3. Two of these mutants were insertions at the N and C termini of VP3, suggesting that both ends of VP3 play a role that is important for capsid assembly or stability. Several class 2 and 3 mutants produced capsids that were unstable during purification of viral particles. One mutant, R432A, made only empty capsids, presumably due to a defect in packaging viral DNA. Additionally, five mutants were defective in heparan binding, a step that is believed to be essential for viral entry. These were distributed into two amino acid clusters in what is likely to be a cell surface loop in the capsid protein VP3. The first cluster spanned amino acids 509 to 522; the second was between amino acids 561 and 591. In addition to the heparan binding clusters, hemagglutinin epitope tag insertions identified several other regions that were on the surface of the capsid. These included insertions at amino acids 1, 34, 138, 266, 447, 591, and 664. Positions 1 and 138 were the N termini of VP1 and VP2, respectively; position 34 was exclusively in VP1; the remaining surface positions were located in putative loop regions of VP3. The remaining mutants, most of them partially defective, were presumably defective in steps of viral entry that were not tested in the preliminary screening, including intracellular trafficking, viral uncoating, or coreceptor binding. Finally, in vitro experiments showed that insertion of the **serpin** receptor ligand in the N-terminal regions of VP1 or VP2 can change the tropism of AAV. Our results provide information on AAV capsid functional domains and are useful for future design of AAV vectors for targeting of specific tissues.

L14 ANSWER 36 OF 49 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000030555 EMBASE
TITLE: Improved production of adenovirus vectors expressing apoptotic transgenes.
AUTHOR: Bruder J.T.; Appiah A.; Kirkman III W.M.; Chen P.; Tian J.; Reddy D.; Brough D.E.; Lizonova A.; Kovesdi I.
CORPORATE SOURCE: Dr. J.T. Bruder, Gen Vec, Inc., 65 W. Watkins Mill Road, Gaithersburg, MD 20878, United States. bruder@genvec.com
SOURCE: Human Gene Therapy, (2000) 11/1 (139-149).
Refs: 53
ISSN: 1043-0342 CODEN: HGTHE3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
016 Cancer
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Adenovirus vectors expressing gene products that can induce apoptosis have potential utility in **gene therapy** applications ranging from the treatment of proliferative diseases to transplantation. However,

adenovirus vectors carrying proapoptotic gene products are difficult to produce, as the apoptotic environment is not conducive to adenovirus gene expression and replication. Production of AdFasL/G, an adenovirus vector that expresses high levels of Fas ligand, was severely reduced in the 293 packaging cell line. Increased yields of AdFasL/G were achieved by inclusion of peptide-based caspase inhibitors in the growth medium. However, use of these inhibitors for large-scale production would be difficult and expensive. A screen for gene products that increase the yield of AdFasL/G in 293 cells revealed that the poxvirus **serpin** CrmA and the adenovirus 14.7K product were able to increase virus yields significantly. Apoptosis induced by AdFasL/G was attenuated in 293CrmA cell lines and virus titers were increased dramatically. However, serial passage of AdFasL/G on 293CrmA cells resulted in the generation of replication-competent adenovirus. To resolve this problem, the CrmA gene was introduced into AE25 cells, an E1-complementing cell line that has limited sequence identity with the vectors. AdFasL/G titers were increased 100-fold on AE25CrmA cells relative to the AE25 cells and RCA contamination was not detectable. In addition, adenovirus vectors that express FADD, caspase 8, and Fas/APO1 were produced efficiently in AE25CrmA and 293CrmA.

L14 ANSWER 37 OF 49 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999076544 EMBASE
TITLE: Development of animal models for adeno-associated virus site-specific integration.
AUTHOR: Rizzuto G.; Gorgoni B.; Cappelletti M.; Lazzaro D.; Gloaguen I.; Poli V.; Sgura A.; Cimini D.; Ciliberto G.; Cortese R.; Fattori E.; La Monica N.
CORPORATE SOURCE: N. La Monica, IRBM, P. Angeletti, 00040 Pomezia, Italy. lamonica@irbm.it
SOURCE: Journal of Virology, (1999) 73/3 (2517-2526).
Refs: 51
ISSN: 0022-538X CODEN: JOVIAM
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The adeno-associated virus (AAV) is unique in its ability to target viral DNA integration to a defined region of human chromosome 19 (AAVS1). Since AAVS1 sequences are not conserved in a rodent's genome, no animal model is currently available to study AAV-mediated site-specific integration. We describe here the generation of transgenic rats and mice that carry the AAVS1 3.5-kb DNA fragment. To test the response of the transgenic animals to Rep- mediated targeting, primary cultures of mouse fibroblasts, rat hepatocytes, and fibroblasts were infected with wild-type wt AAV. PCR amplification of the inverted terminal repeat (ITR)-AAVS1 junction revealed that the AAV genome integrated into the AAVS1 site in fibroblasts and hepatocytes. Integration in rat fibroblasts was also observed upon transfection of a plasmid containing the rep gene under the control of the p5 and **p19** promoters and a dicistronic cassette carrying the green fluorescent protein (GFP) and neomycin (neo) resistance gene between the ITRs of AAV. The localization of the GFP-Neo sequence in the AAVS1 region was determined by Southern blot and FISH analysis. Lastly, AAV genomic DNA integration into the AAVS1 site in vivo was assessed by virus injection into the quadriceps muscle of transgenic rats and mice. Rep-mediated targeting to the AAVS1 site was detected in several injected animals. These results indicate that the transgenic lines are proficient for Rep-mediated targeting. These animals should allow further characterization of the molecular aspects of site-specific integration and testing of the efficacy of targeted integration of AAV recombinant vectors designed for human **gene therapy**.

L14 ANSWER 38 OF 49 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97300024 EMBASE
DOCUMENT NUMBER: 1997300024
TITLE: Gene transfer into hepatoma cell lines via the serpin enzyme complex receptor.
AUTHOR: Ziady A.-G.; Perales J.C.; Ferkol T.; Gerken T.; Beegen H.; Perlmutter D.H.; Davis P.B.

CORPORATE SOURCE: P.B. Davis, Dept. of Pediatrics, Case Western Reserve Univ., 11100 Euclid Ave., Cleveland, OH 44106, United States
SOURCE: American Journal of Physiology - Gastrointestinal and Liver Physiology, (1997) 273/2 36-2 (G545-G552).
Refs: 32
ISSN: 0193-1857 CODEN: APGPDF
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The **serpin** enzyme complex receptor (SECR) expressed on hepatocytes binds to a conserved sequence in .alpha.1-antitrypsin (.alpha.1-AT) and other **serpins**. A molecular conjugate consisting of a synthetic peptide (C1315) based on the SECR binding motif of human .alpha.1-AT covalently coupled to poly-L-lysine was used to introduce reporter genes into hepatoma cell lines in culture. This conjugate condensed DNA into spheroidal particles 18-25 nm in diameter. When transfected with the SECR-directed complex containing pGL3, Hep G2 cells that express the receptor, but not Hep G2 cells that do not, expressed a peak luciferase activity of 538,731 .+-. 144,346 integrated light units/mg protein 4 days after transfection. Free peptide inhibited uptake and expression in a dose-dependent manner. Complexes of DNA condensed with polylysine or LC- sulfo-N-succinimidyl-3-(2-pyridyldithio)propionate-substituted polylysine were ineffective. Transfection with a plasmid encoding human factor IX produced expression in Hep G2 (high) and HuH7 cells that express SECR but not Hep G2 (low) cells that lack the receptor. Fluorescein-labeled C1315 peptide labeled 9-31% of Hep G2 (high), 10-14% of HUH7, and 0.6-3.4% of Hep G2 (low) cells, and when the lac Z gene was transfected, only these cells expressed .beta.-galactesidase. SECR-mediated gene transfer gives efficient, specific uptake and high-level expression of three reporter genes, and the system merits further study for **gene therapy**.

L14 ANSWER 39 OF 49 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97295930 EMBASE
DOCUMENT NUMBER: 1997295930
TITLE: Adenovirus-mediated delivery of human kallistatin gene reduces blood pressure of spontaneously hypertensive rats.
AUTHOR: Chen L.-M.; Chao L.; Chao J.
CORPORATE SOURCE: Dr. J. Chao, Dept. Biochemistry Molecular Biology, Medical University of South Carolina, 171 Ashley Avenue, Charleston, SC 29425, United States
SOURCE: Human Gene Therapy, (1997) 8/3 (341-347).
Refs: 21
ISSN: 1043-0342 CODEN: HGTHE3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
030 Pharmacology
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Human kallistatin, or human tissue kallikrein-binding protein (HKBP), is a serine proteinase inhibitor (**serpin**). Transgenic mice overexpressing rat kallikrein-binding protein are hypotensive. To elucidate therapeutic potentials of kallistatin in hypertension, the human kallistatin gene in an adenoviral vector was directly introduced into spontaneously hypertensive rats (SHR) through portal vein injection. The kallistatin cDNA construct (RSV-cHKBP) under the promoter control of Rous sarcoma virus 3' long terminal repeat (LTR) was incorporated into adenovirus (Ad.RSV-cHKBP). Recombinant kallistatin in 293 cells transfected with RSV-cHKBP or Ad.RSV-cHKBP was measured by ELISA and by its complex formation with tissue kallikrein. A single intraportal vein injection of Ad.RSV-cHKBP at a dose of 8 x 1010 pfu results in a significant reduction of blood pressure of SHR for 4 weeks. Human kallistatin mRNA was detected in the liver, spleen, kidney, aorta, and

lung of rats receiving gene delivery. Immunoreactive human kallistatin in rat serum was detected at the highest level 1 day post injection and at lesser amounts in rat tissues. This study shows that adenovirus harboring Ad.RSV-cHKBP produces functional kallistatin, and adenovirus-mediated transfer of the human kallistatin gene reduces blood pressures of SHR. The results suggest that kallistatin may function as a vasodilator in vivo and provide important information for a potential **gene therapy** approach to hypertension.

L14 ANSWER 40 OF 49 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:326621 BIOSIS
DOCUMENT NUMBER: PREV200200326621
TITLE: RNA interference by expression of short-interfering RNAs and hairpin RNAs in mammalian cells.
AUTHOR(S): Yu, Jenn-Yah; DeRuiter, Stacy L.; Turner, David L. (1)
CORPORATE SOURCE: (1) University of Michigan, 1150 West Medical Center Drive, C560 MSRB II, Ann Arbor, MI, 48109-0669: dlturner@umich.edu USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (April 30, 2002) Vol. 99, No. 9, pp. 6047-6052. http://www.pnas.org. print.
ISSN: 0027-8424.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Duplexes of 21-nt RNAs, known as short-interfering RNAs (siRNAs), efficiently inhibit gene expression by RNA interference (RNAi) when introduced into mammalian cells. We show that siRNAs can be synthesized by in vitro transcription with T7 RNA polymerase, providing an economical alternative to chemical synthesis of siRNAs. By using this method, we show that short hairpin siRNAs can function like siRNA duplexes to inhibit gene expression in a sequence-specific manner. Further, we find that hairpin siRNAs or siRNAs expressed from an RNA polymerase III vector based on the mouse U6 RNA promoter can effectively inhibit gene expression in mammalian cells. U6-driven hairpin siRNAs dramatically reduced the expression of a neuron-specific beta-tubulin protein during the neuronal differentiation of mouse **P19** cells, demonstrating that this approach should be useful for studies of differentiation and neurogenesis. We also observe that mismatches within hairpin siRNAs can increase the strand selectivity of a hairpin siRNA, which may reduce self-targeting of vectors expressing siRNAs. Use of hairpin siRNA expression vectors for RNAi should provide a rapid and versatile method for assessing gene function in mammalian cells, and may have applications in **gene therapy**.

L14 ANSWER 41 OF 49 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:523061 BIOSIS
DOCUMENT NUMBER: PREV200100523061
TITLE: Histological evaluation of lentiviral vector mediated gene transfer in explants from retinal degenerative (rd) mice.
AUTHOR(S): Blanks, J. C. (1); Pang, J. (1); Cheng, M. (1); Day, S.; Planelles, V.
CORPORATE SOURCE: (1) Eye Res Inst, Oakland Univ, Rochester, MI USA
SOURCE: Society for Neuroscience Abstracts, (2001) Vol. 27, No. 1, pp. 958. print.
Meeting Info.: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB To compare the transduction efficiency of a lentiviral vector in rd mice at various ages, retinal explants from postnatal days (P) 3 to **P19** rd mice were infected with a lentiviral vector with a green fluorescence protein (GFP) reporter gene (pHR-CMV-GFP). Retinal explant was prepared, flattened on a Millipore insert (photoreceptor-side down) and placed in a six-well tissue culture plate. Each well contained 0.6ml of DMEM containing 10% FCS plus Fungizone (1.25 mg/ml). For each explant, 30ml of vector (1.0X10 of 7 infectious units/ml) was placed directly on the ganglion cell surface. Controls consisted of 30ml of DMEM, placed directly on the ganglion cell surfac. Retinal explants were infected for 24 hours,

then rinsed and incubated in vector-free media for 4 days in vitro (DIV). Media was replenished daily. After 5 DIV, retinal explants were lightly fixed, embedded and sectioned for light microscopy. Fluorescence could be detected near the edge of the explants from all retinas treated with vector. Fluorescence increased from P3 to P7 and appeared in a larger portion of the explant surface in P5 and P7, then declined; by **P19** only sparse fluorescence at the explant edge remained. No fluorescence was detected in control retinas. Histological examination showed fluorescent cells located primarily in the photoreceptor (PR) cell layer from P3-P9. The largest number of fluorescent PR cells were observed in P5 and P7 explants. Transduced PR cells were completely filled with GFP. This result suggests a suitable time to start the lentivirus-mediated **gene therapy** on rd mice.

L14 ANSWER 42 OF 49 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:504055 BIOSIS
DOCUMENT NUMBER: PREV200100504055
TITLE: Characterization of permanent cell lines that contain the AAV2 rep-cap genes on an Epstein-Barr-virus-based episomal plasmid.
AUTHOR(S): Neyns, Bart; Vermeij, Joanna; Teugels, Eric; De Rijcke, Martine; Hermonat, Paul; De Greve, Jacques (1)
CORPORATE SOURCE: (1) Oncologisch Centrum, Akademisch Ziekenhuis, Vrije Universiteit Brussel, Laarbeeklaan 101, B-1090, Brussels: ongdgej@az.vub.ac.be Belgium
SOURCE: Intervirology, (July August, 2001) Vol. 44, No. 4, pp. 255-263. print.
ISSN: 0300-5526.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Recombinant adeno-associated virus (rAAV) has emerged as a promising **gene therapy** vector. Its development, however, has been hampered by the lack of a readily available efficient production method. We investigated the possibility of establishing permanent cell lines for the production of rAAV with a new Epstein-Barr-virus (EBV)-based episomal AAV rep-cap plasmid (pCEP-rep/cap). HeLa and 293 cells were stably transfected with plasmids that carry the AAV2 rep/cap genes under transcriptional control of their endogenous promoters (p5, **p19** and p40) either on the pCEP-rep/cap or an integrated (pIM45) plasmid. For the ease of monitoring transgene expression in live cells, a rAAV vector expressing gfp (the green fluorescent protein gene, rAAV-gfp/neo) was used. Establishment of stable transfected cell lines with these plasmids proved feasible but their usefulness was limited because of their instability. Within 8-12 weeks after their establishment, stably transfected rep-cap cell lines invariably lost their function. In addition, the rAAV-gfp/neo vector we used was susceptible to mutation in stably transfected HeLa cells. Our observations demonstrate specific problems both at the level of rep/cap gene function and the rAAV genome that can occur with the establishment of rAAV production cell lines. These experiments should aid the further development of efficient rAAV production protocols.

L14 ANSWER 43 OF 49 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:285839 BIOSIS
DOCUMENT NUMBER: PREV200100285839
TITLE: Endogenous angiogenesis inhibitors and their therapeutic implications.
AUTHOR(S): Cao, Yihai (1)
CORPORATE SOURCE: (1) Laboratory of Angiogenesis Research, Microbiology and Tumor Biology Center, Karolinska Institute, S-171 77, Stockholm: yihai.cao@mtc.ki.se Sweden
SOURCE: International Journal of Biochemistry & Cell Biology, (April, 2001) Vol. 33, No. 4, pp. 357-369. print.
ISSN: 1357-2725.
DOCUMENT TYPE: General Review
LANGUAGE: English
SUMMARY LANGUAGE: English
AB A number of endogenous inhibitors targeting the tumor vasculature have recently been identified using in vitro and in vivo antiangiogenesis

models. While many of these angiogenesis inhibitors display a broad spectrum of biological actions on several systems in the body, several inhibitors including angiostatin, endostatin, and **serpin** antithrombin seem to act specifically on the proliferating endothelial cell compartment of the newly formed blood vessels. The discovery of these specific endothelial inhibitors not only increases our understanding of the functions of these molecules in the regulation of physiological and pathological angiogenesis, but may also provide an important therapeutic strategy for the treatment of cancer and other angiogenesis dependent diseases, including diabetic retinopathy and chronic inflammations. Systemic administration of these angiogenesis inhibitors in animals significantly suppresses the growth of a variety of tumors and their metastases. However, their production as functional recombinant proteins has been proven to be difficult. In addition, high dosages of these inhibitors are required to suppress tumor growth in animal studies. Other disadvantages of the antiangiogenic protein therapy include repeated injections, prolonged treatment, transmission of toxins and infectious particles, and high cost for manufacturing large amounts of protein molecules. Thus, alternative strategies need to be developed in order to improve the clinical settings of antiangiogenic therapy. Developments of these strategies are ongoing and they include identification of more potent inhibitors, antiangiogenic **gene therapy**, improvement of protein/compound half-lives in the circulation, increase of their concentrations at the disease location, and combinatorial therapies with approaches including chemotherapy, radiotherapy, and immunotherapy. Despite the above-mentioned disadvantages, a few inhibitors have entered into the early stages of clinical trials and they may bring new hopes for the treatment of cancer and other angiogenesis dependent diseases.

L14 ANSWER 44 OF 49 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:97117 BIOSIS
DOCUMENT NUMBER: PREV200100097117
TITLE: Gene therapy and protease inhibition in neurodegeneration: transfection of motor neurons with protease nexin I.
AUTHOR(S): Dalal, R. (1); Samson, F. E.; Suo, Z.; Citron, B. A.; Landis, M.; Graeser, R.; Festoff, B. W.
CORPORATE SOURCE: (1) VA Medical Ctr., Kansas City, MO USA
SOURCE: Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-307.8. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000 Society for Neuroscience
. ISSN: 0190-5295.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Roles for the serine protease:**serpin** balance are clear in the CNS and at the peripheral neuromuscular synapse (NMJ). We have investigated the **serpin**, PNI, a potent tissue inhibitor of thrombin, that is highly localized at NMJs. In previous studies, PNI dimers were less expressed and surface-localized just prior to and after the period of polyneuronal synapse elimination in postnatal skeletal muscle. In addition, although PNI protein was detected in adult rat motor neurons (MNs) PNI message was absent. Finally, although a parent neuroblastoma expressed PNI mRNA, a hybrid cell fused with murine embryonic MNs did not. Since thrombin is one of the earliest signals inducing neuronal apoptosis in neurodegenerative and traumatic disorders it is a prime target for therapeutic intervention. Using pTsign we generated a fusion construct between PNI and GFP and tested first for expression of PNI and secondly for neuroprotection afforded by this **gene therapy** of MNs harboring this construct. We used simultaneous confocal visualization of GFP and apoptotosis specific markers and confirmed the elevated expression of PNI in these cells. We then examined cells for reduction in apoptosis induced by thrombin and other agents. Preliminary evidence suggests this may be a productive approach to manipulating synaptic apoptosis in neurodegenerative conditions.

L14 ANSWER 45 OF 49 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:408876 BIOSIS

DOCUMENT NUMBER: PREV200000408876
TITLE: Mutational analysis of the adeno-associated virus type 2 (AAV2) capsid gene and construction of AAV2 vectors with altered tropism.
AUTHOR(S): Wu, Pei; Xiao, Wu; Conlon, Thomas; Hughes, Jeffrey; Agbandje-McKenna, Mavis; Ferkol, Thomas; Flotte, Terence; Muzyczka, Nicholas (1)
CORPORATE SOURCE: (1) Department of Molecular Genetics and Microbiology, College of Medicine, University of Florida, Gainesville, FL, 32610 USA
SOURCE: Journal of Virology, (September, 2000) Vol. 74, No. 18, pp. 8635-8647. print.
ISSN: 0022-538X.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Adeno-associated virus type 2 (AAV2) has proven to be a valuable vector for **gene therapy**. Characterization of the functional domains of the AAV capsid proteins can facilitate our understanding of viral tissue tropism, immunoreactivity, viral entry, and DNA packaging, all of which are important issues for generating improved vectors. To obtain a comprehensive genetic map of the AAV capsid gene, we have constructed 93 mutants at 59 different positions in the AAV capsid gene by site-directed mutagenesis. Several types of mutants were studied, including epitope tag or ligand insertion mutants, alanine scanning mutants, and epitope substitution mutants. Analysis of these mutants revealed eight separate phenotypes. Infectious titers of the mutants revealed four classes. Class 1 mutants were viable, class 2 mutants were partially defective, class 3 mutants were temperature sensitive, and class 4 mutants were noninfectious. Further analysis revealed some of the defects in the class 2, 3, and 4 mutants. Among the class 4 mutants, a subset completely abolished capsid formation. These mutants were located predominantly, but not exclusively, in what are likely to be beta-barrel structures in the capsid protein VP3. Two of these mutants were insertions at the N and C termini of VP3, suggesting that both ends of VP3 play a role that is important for capsid assembly or stability. Several class 2 and 3 mutants produced capsids that were unstable during purification of viral particles. One mutant, R432A, made only empty capsids, presumably due to a defect in packaging viral DNA. Additionally, five mutants were defective in heparan binding, a step that is believed to be essential for viral entry. These were distributed into two amino acid clusters in what is likely to be a cell surface loop in the capsid protein VP3. The first cluster spanned amino acids 509 to 522; the second was between amino acids 561 and 591. In addition to the heparan binding clusters, hemagglutinin epitope tag insertions identified several other regions that were on the surface of the capsid. These included insertions at amino acids 1, 34, 138, 266, 447, 591, and 664. Positions 1 and 138 were the N termini of VP1 and VP2, respectively; position 34 was exclusively in VP1; the remaining surface positions were located in putative loop regions of VP3. The remaining mutants, most of them partially defective, were presumably defective in steps of viral entry that were not tested in the preliminary screening, including intracellular trafficking, viral uncoating, or coreceptor binding. Finally, in vitro experiments showed that insertion of the **serpin** receptor ligand in the N-terminal regions of VP1 or VP2 can change the tropism of AAV. Our results provide information on AAV capsid functional domains and are useful for future design of AAV vectors for targeting of specific tissues.

L14 ANSWER 46 OF 49 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:397947 BIOSIS
DOCUMENT NUMBER: PREV200000397947
TITLE: InK4c-p18 and InK4d-p19, inhibitors of cyclin-dependent kinases CDK4 and CDK6, and uses thereof.
AUTHOR(S): Sherr, Charles J. (1); Downing, James; Hirai, Hiroshi; Okuda, Tsukasa
CORPORATE SOURCE: (1) Memphis, TN USA
ASSIGNEE: St. Jude Children's Research Hospital, Memphis, TN, USA
PATENT INFORMATION: US 6033847 March 07, 2000
SOURCE: Official Gazette of the United States Patent and Trademark

Office Patents, (Mar. 7, 2000) Vol. 1232, No. 1, pp. No pagination. e-file.
ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
AB Members of the InK4 (Inhibitors of CDK4) family inhibit the activities of specific cyclin D-dependent kinases (CDK4 and/or CDK6), thereby arresting cell cycle progression in G1 phase and preventing chromosomal DNA replication. Disclosed herein are novel mammalian InK4 family members, having apparent molecular masses of 18,000 and 19,000 daltons, designated "InK4c-p18" and "InK4d-**p19**," respectively, or simply "p18" and "**p19**." In particular, the invention provides **p19** genes and proteins isolated from murine or human cells and p18 genes and proteins from murine cells. When constitutively expressed in cells, **p19** inhibits cyclin D-dependent kinase activity in vivo and induces G1 phase arrest. Materials and methods disclosed herein include (1) nucleic acids that encode p18 or **p19**; (2) methods for detecting nucleic acids encoding p18 or **p19** proteins; (3) methods for producing p18 or **p19** proteins using nucleic acids that encode p18 or **p19**, respectively; (4) purified p18 or **p19** proteins and peptide fragments, oligopeptides, or fusion proteins derived therefrom; (5) methods of inhibiting cells from replicating their chromosomal DNA using purified p18 or **p19** proteins or derivatives thereof; (6) antibodies that specifically bind p18 or **p19**; (7) methods for detecting p18 and **p19** proteins; (8) methods of stimulating cell growth by blocking p18 or **p19** expression via antisense oligonucleotides; (9) methods of **gene therapy** using nucleic acids that encode p18 or **p19**; and (10) methods of making transgenic non-human animals that have alterations in the gene encoding p18 or **p19**, or in both genes.

L14 ANSWER 47 OF 49 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:129583 BIOSIS
DOCUMENT NUMBER: PREV200000129583
TITLE: Improved production of adenovirus vectors expressing apoptotic transgenes.
AUTHOR(S): Bruder, Joseph T. (1); Appiah, Angela; Kirkman, Wayne M., III; Chen, Ping; Tian, Jie; Reddy, Damodar; Brough, Douglas E.; Lizonova, Alena; Kovesdi, Imre
CORPORATE SOURCE: (1) GenVec, Inc., 65 W. Watkins Mill Road, Gaithersburg, MD, 20878 USA
SOURCE: Human Gene Therapy., (Jan. 1, 2000) Vol. 11, No. 1, pp. 139-149.
ISSN: 1043-0342.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Adenovirus vectors expressing gene products that can induce apoptosis have potential utility in **gene therapy** applications ranging from the treatment of proliferative diseases to transplantation. However, adenovirus vectors carrying proapoptotic gene products are difficult to produce, as the apoptotic environment is not conducive to adenovirus gene expression and replication. Production of AdFasL/G, an adenovirus vector that expresses high levels of Fas ligand, was severely reduced in the 293 packaging cell line. Increased yields of AdFasL/G were achieved by inclusion of peptide-based caspase inhibitors in the growth medium. However, use of these inhibitors for large-scale production would be difficult and expensive. A screen for gene products that increase the yield of AdFasL/G in 293 cells revealed that the poxvirus **serpin** CrmA and the adenovirus 14.7K product were able to increase virus yields significantly. Apoptosis induced by AdFasL/G was attenuated in 293CrmA cell lines and virus titers were increased dramatically. However, serial passage of AdFasL/G on 293CrmA cells resulted in the generation of replication-competent adenovirus. To resolve this problem, the CrmA gene was introduced into AE25 cells, an E1-complementing cell line that has limited sequence identity with the vectors. AdFasL/G titers were increased 100-fold on AE25CrmA cells relative to the AE25 cells and RCA contamination was not detectable. In addition, adenovirus vectors that express FADD, caspase 8, and Fas/APO1 were produced efficiently in